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DISEASES OF CHILDREN

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Differential Diagnosis of Tumors and Tumor-like Lesions of Liver in Infancy and Childhood
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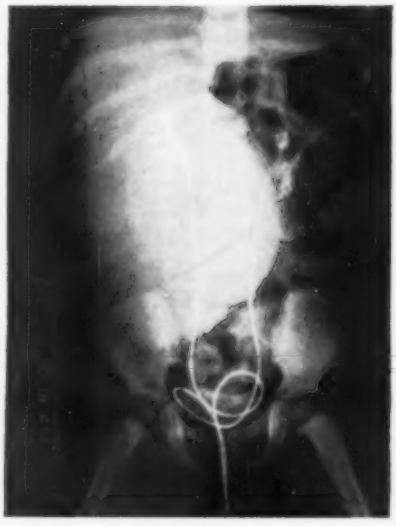

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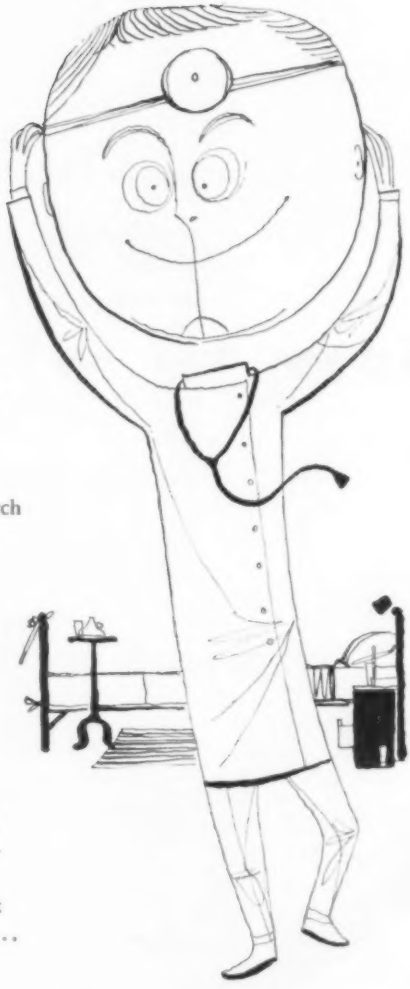

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Glycogen-Storage Disease

A Study on the Effect of Sodium *l*-Thyroxine and Glucagon

NINA KOULISCHER, M.D.
and
DONALD E. PICKERING, M.D., San Francisco
With the Technical Assistance of Margaret Cole, B.A., M.S.

INTRODUCTION

Glycogen-storage disease is a congenital defect of carbohydrate metabolism characterized by deficient glycolysis and associated glycogen accumulation in various organs, particularly the liver. Secondary manifestations relate to the primary site of involvement. When the defect is principally in the liver, there is a propensity for hypoglycemia and exaggerated lipogenesis with secondary ketosis.

The hepatic form of the disease, the first described,* is severest when manifest in the neonatal period.† Various other clinical types of the syndrome, not to be considered in this publication, have been described.‡

Glycogen-storage disease appears to be familial, and the specific enzymatic defect or anomaly is presumably inherited as a simple recessive trait.§ This defect would appear to involve chiefly glucose-6-phosphatase. Substantial support for this thesis exists in the observations of Thannhauser and co-workers [11] and Cori and associates,‖ who demonstrated low or absent glucose-6-phosphatase activity in liver preparations from several cases of classical von Gierke's disease. Manifestations of the defect generally follow the tissue distribution of glucose-6-phosphatase.[14] In 2 out of 10 cases, an abnormal glycogen structure has also been demonstrated.[15] Therapeutic attempts have included chiefly the use of a high-protein diet, frequent feedings, and corticotropin (ACTH) and corticoids.¶

We have studied three children (two are siblings) with the hepatic form of the syndrome, placing particular emphasis upon the development of a therapeutic regimen which might (1) provide the maximum possible caloric intake from protein; (2) avoid carbohydrates which can be utilized only following conversion in liver (i. e., a galactose-free diet); and (3) increase phosphatase activity.

METHODS

Metabolic studies in these children included (*a*) four-hour glucose and galactose tolerance tests (after the oral administration of 2 gm. per kilogram of body weight of either substance); (*b*)

Submitted for publication Nov. 9, 1955.

Presented in part at the Western Society for Pediatric Research meeting, Oct. 19, 1955, at Portland, Ore.

After March 1, 1956, Dr. Pickering's address: Department of Pediatrics, University of Oregon School of Medicine, Portland, Ore.

Support for this study has been given by the Cox Fund (171), the Research Committee, and the Mary H. K. Welsh Endowment Fund to the University of California Medical Center.

Dazian Foundation Fellow (Dr. Koulischer) for Medical Research and from the Pediatric Endocrine and Metabolic Laboratory, Department of Pediatrics, University of California Medical Center.

* References 1 and 2.

† References 3-5.

‡ References 3 and 6-9.

§ References 4, 9, and 10.

‖ References 12 and 13.

¶ References 9 and 16-18.

epinephrine tolerance tests (following the subcutaneous administration of 0.03 ml. per kilogram of 1:1000 epinephrine); (*c*) insulin sensitivity tests (following the intravenous administration of 0.05 unit of regular insulin per kilogram); (*d*) glucagon # tolerance tests (following the intramuscular administration of 0.25 mg. of glucagon per kilogram), and (*e*) repeated fasting blood sugar determinations.

All studies were conducted after an eight-hour fast. Glucose was determined by a micromodification of the method described by Nelson[19] (Somogyi) and galactose by a modification of the method described by Althausen and co-workers.[20]

The following high-protein, galactose-free diet was employed: Infants—25% of caloric requirements was supplied by protein, 25% by fat, and 50% by carbohydrates. The basic formula consisted of 15 fluid ounces (443.6 ml.) of soybean milk, 15 fluid ounces of water, 3½ oz. (97.2 gm.) of baby liver or osterized freshly cooked liver, and 1 beaten raw egg. Older children—25% of caloric requirements was again supplied by protein, with the percentage of Calories from fat increased for palatability. Soybean milk was used in place of cow's milk, and soybean bread or other bread made without milk was prescribed.

Eggs, meat, cheese, washed large-curd cottage cheese, 10% fruits, and 5% vegetables made up the remainder of the diet. All fruits were cooked or canned without sugar.

In addition to three meals a day midmorning, midafternoon, and bedtime snacks were offered.

Sodium *l*-thyroxine was administered daily orally as 0.1 mg. tablets, prepared at this medical center.

REPORT OF CASES

Case 1.—A white baby girl was first admitted to the University of California Hospital at the age of 10 months. She had seemed well until the age of 5 months, when abdominal enlargement was first noted. Progression of this and associated symptoms led to the diagnosis of celiac syndrome in another hospital at the age of 8 months. With the institution of a high-protein, celiac type diet she showed moderate improvement, but because of persisting hepatomegaly and poor weight gain she was referred to this hospital.

Examination on admission revealed a pale, moderately dehydrated infant with wasted extremities and a protuberant abdomen, who weighed 7700 gm. Her height was 70 cm., which is the 50th percentile for 9 months. The liver edge was palpable 6 cm. below the right costal margin. The remainder of the examination was not remarkable. Urinalysis revealed no acetone or reducing substance. There was no elevation of blood sugar following the administration of epinephrine. However, the diagnosis of glycogen-storage disease was not made until a subsequent admission at the age of 2 years, when an exploratory laparotomy and liver biopsy were performed. She was then placed on a high-protein, galactose-free diet and interval feedings.

She was readmitted at the age of 3 years 3 months for our study. During the preceding year

Fig. 1.—Case 1.

she had taken the diet well and had generally improved. Growth, however, had been slower than normal. Her height was 80 cm., which is 8.4 cm. below the 3rd percentile for 3 years; weight was 13000 gm., which is the 25th percentile for 5 years. Examination again revealed a somewhat pale child with a protuberant abdomen. The liver edge was felt 6 to 8 cm. below the right costal margin. At the completion of our studies, 0.15 mg. of sodium *l*-thyroxine daily was added to the regimen.

Six weeks later, she was readmitted for repeat studies. In the interval, her mother had noted a

Glucagon used in these studies was provided by Dr. W. R. Kirtley, of Eli Lilly & Company, Research Laboratories, Indianapolis.

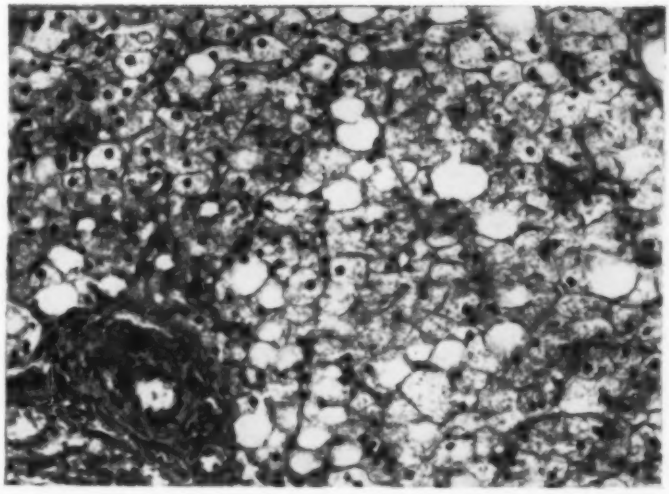

Fig. 2. — Photomicrograph of liver biopsy specimen in Case 1. The hepatic cells are distended with finely reticulated cytoplasm representing glycogen. In addition, scattered parenchymal cells exhibit a single large clear cytoplasmic vacuole representing fat. There is no evidence of inflammation or fibrosis.

decrease in the size of her abdomen. She was now able to wear clothes that previously had been too small. She had become more alert and had more energy. Examination was essentially unchanged from her previous entry. The liver still was extended 6 to 8 cm. below the right costal margin. The urine was negative for acetone and reducing substance.

Fig. 3.—Case 2.

CASE 2.—A white baby girl, a younger sister of Case 1, was first admitted to the University of California Hospital at the age of 8 months because of recently noted hepatomegaly and the established diagnosis of von Gierke's disease in her older sibling. Weight gain had ceased at the age of 6 months.

Examination on admission revealed a moderately dehydrated chronically ill-appearing infant weighing 6700 gm., with a protuberant abdomen. The liver edge was palpable 6 cm. below the right costal margin. Urine examination revealed acetone but no reducing substance. She had a urinary infection (Escherichia coli) which cleared with appropriate antibiotic therapy. The patient was investigated for possible glycogen-storage disease, and the diagnosis was confirmed. She was discharged on a high-protein ,galactose-free diet with interval feedings and 0.1 mg. of sodium *l*-thyroxine daily.

Six weeks later, she was readmitted for repeat studies. In the interval, she had improved generally and had gained 700 gm. The liver still extended approximately 6 cm. below the right costal margin. Her urine was negative for acetone and reducing substance.

CASE 3.—A Japanese-American baby girl was first referred to the University of California Hospital at the age of 9 months because of the recent finding of hepatomegaly and poor weight gain.

Examination on admission revealed a chubby infant with a markedly protuberant abdomen, weighing 8100 gm. The liver was enlarged generally and extended to the right iliac crest. Her urine was positive for acetone and gave an olive

Fig. 4.—Case 3.

reduction. Exploratory laparotomy and liver biopsy were performed. Microscopic examination was compatible with the diagnosis of von Gierke's disease. The patient was discharged on a high-protein, galactose-free diet and interval feedings.

She was readmitted one month later for further investigation. In the interval, she had taken her diet well and had gained 700 gm. Her liver was smaller than on the previous examination. Her urine was negative for acetone and reducing substance. She was discharged, and was readmitted six weeks later for repeat studies. In the interim she had remained on the same diet and, in addition, had received 0.1 mg. of sodium *l*-thyroxine daily. She had continued to do well, and her parents felt that her abdomen had become smaller.

Examination was essentially unchanged from her previous entry. Her urine was still free from acetone and reducing substance.

RESULTS AND COMMENT

These children were found to be rather typical of others reported in their response to the oral administration of glucose and galactose. As data in the left hand block of each patient's graph in Figure 6 indicate, blood sugar concentration rose slowly from low fasting values (46-61 mg. per 100 cc.) to maximum concentrations two and one-half to three times greater within 60 minutes after the ingestion of glucose.

Data plotted to the right in each case represent similar tolerance studies conducted after six weeks of sodium *l*-thyroxine therapy. While there was little demonstrable change in fasting total reducing substance levels, there was a consistently more rapid elevation after sodium *l*-thyroxine administration. This would suggest that the rate of

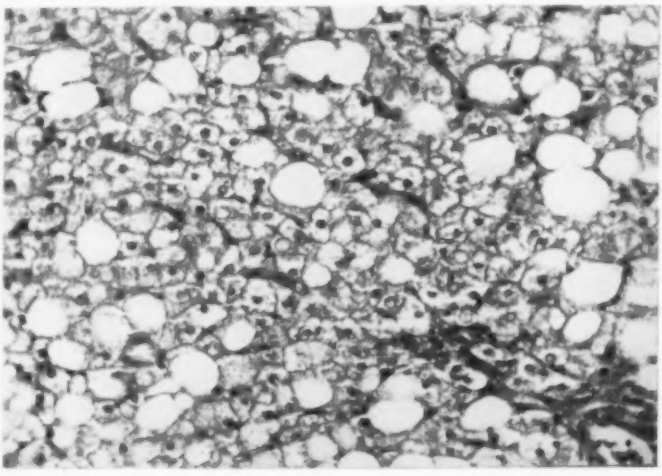

Fig. 5. — Photomicrograph of liver biopsy specimen in Case 3. The hepatic cells show somewhat less glycogen accumulation, while fat-distended cells are more prominent as compared to Figure 2. Note nuclear vacuolation.

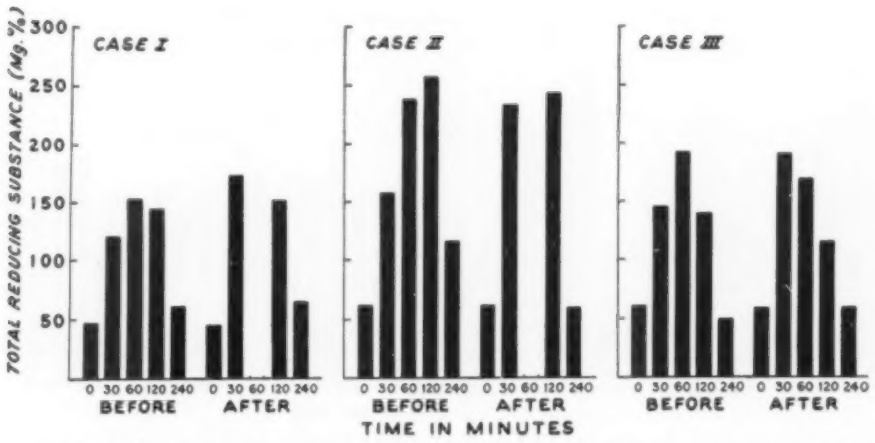

Fig. 6.—Glucose tolerance tests before and after sodium *l*-thyroxine therapy. Each column represents total reducing substance. Note the more rapid rise in blood glucose following thyroxine therapy.

intestinal absorption of glucose was increased with administration of sodium *l*-thyroxine.

Hypoglycemia was present with fasting in all three cases. Moreover, a high proportion of the total reducing substance present was nonfermentable. Wagner has reported similar findings in three cases and has shown that the nonfermentable reducing substance is composed chiefly of the phosphorylated hexoses, glucose-6-phosphate and fructose-6-phosphate.[21] While sodium *l*-thyroxine administration did not appear to alter significantly their total reducing substance with fasting, its use resulted in a very significant reduction in the concentration of nonfermentable reducing substance and a proportionate increase in fermentable reducing substance. This is shown in Figure 7, which compares random fasting values of total reducing substance, fermentable and nonfermentable, before and after six weeks of sodium *l*-thyroxine therapy.

Administration of galactose was not accompanied by abnormal accumulation of galactose in blood either before or after sodium *l*-thyroxine (Fig. 8). It is presumed

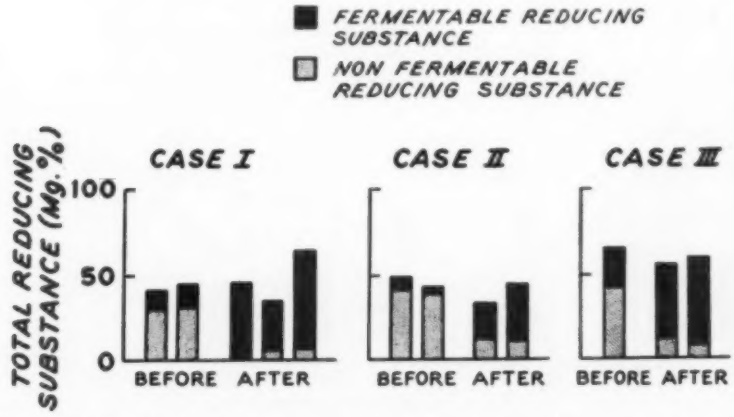

Fig. 7.—Fasting blood sugar before and after sodium *l*-thyroxine therapy, showing the increase in fermentable reducing substance with thyroxine therapy.

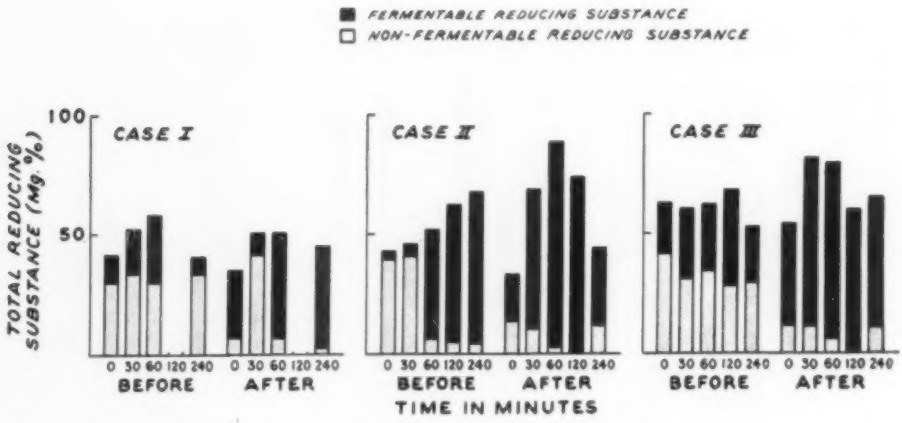

Fig. 8.—Galactose tolerance tests before and after sodium *l*-thyroxine therapy.

that the livers of these children had taken up galactose and stored it as glycogen at a normal rate. This had been demonstrated previously by Mason and Andersen.[3] The reduction in nonfermentable reducing substance as a percentage of total reducing substance after sodium *l*-thyroxine therapy is again shown in Figure 8.

Insulin sensitivity was exaggerated in all three patients. By 30 minutes, the values for blood total reducing substance dropped by more than 50%, and values of 10 to 30 mg. per 100 cc. persisted through a 90-minute period of observation. Clinical manifestations of hypoglycemia consisted of perspiration, pallor, tachycardia, and somnolence. By 130-150 minutes, total reducing substance concentrations had begun to return toward the fasting values. Sensitivity appeared to be less exaggerated after sodium *l*-thyroxine administration, as shown in data from Case 1 (Fig. 9).

The underlying primary pathophysiologic factor in this disease complex, a pronounced enzymatic defect in liver glycolysis, is further demonstrated by studies of the responsiveness of these children to epinephrine and glucagon administration. These two hormones exert their effect by increasing the concentration of active phosphorylase, which

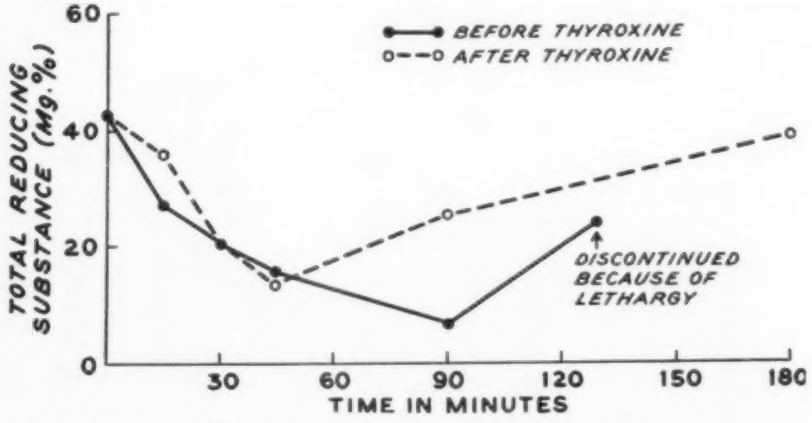

Fig. 9.—Insulin sensitivity before and after sodium *l*-thyroxine administration, showing more rapid recovery following thyroxine.

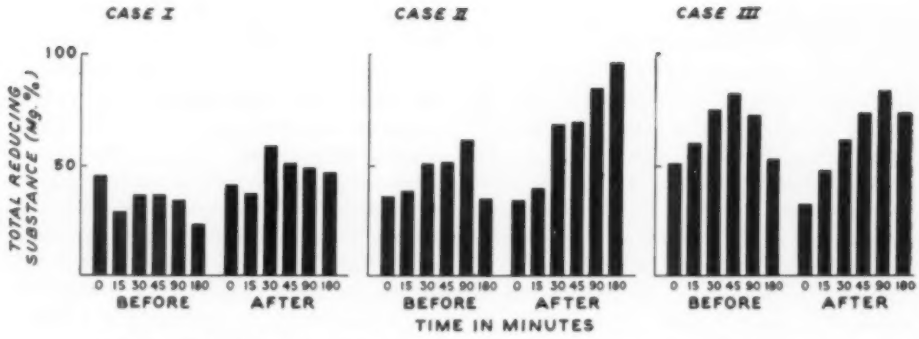

Fig. 10.—Epinephrine tolerance tests before and after sodium *l*-thyroxine therapy.

is considered to be the rate-limiting enzyme in liver glycolysis.* This enzyme has been shown to exist in normal proportions in von Gierke's disease and is not, therefore, implicated. If all enzymes beyond phosphorylase were normal (particularly glucose-6-phosphatase), no obstruction to the action of the hyperglycemic-glycogenolytic factor and epinephrine should have occurred.

Following epinephrine administration (prior to sodium *l*-thyroxine therapy), total reducing substance did not increase in Case 1, and the response in Case 2 and Case 3 was less than observed in normal children of this age. Case 2 demonstrated a significant increase in response to epinephrine following sodium *l*-thyroxine administration. The responsiveness of Case 1 and Case 3 was also increased, but to a smaller degree.

Glucagon, in amounts which cause a pronounced elevation in the blood sugar concentration in normal children, has been found to be significantly less effective in children with classical von Gierke's disease.† Accordingly, in the present study much larger quantities of the hormone were required to

* References 22-24.

† References 5 and 25.

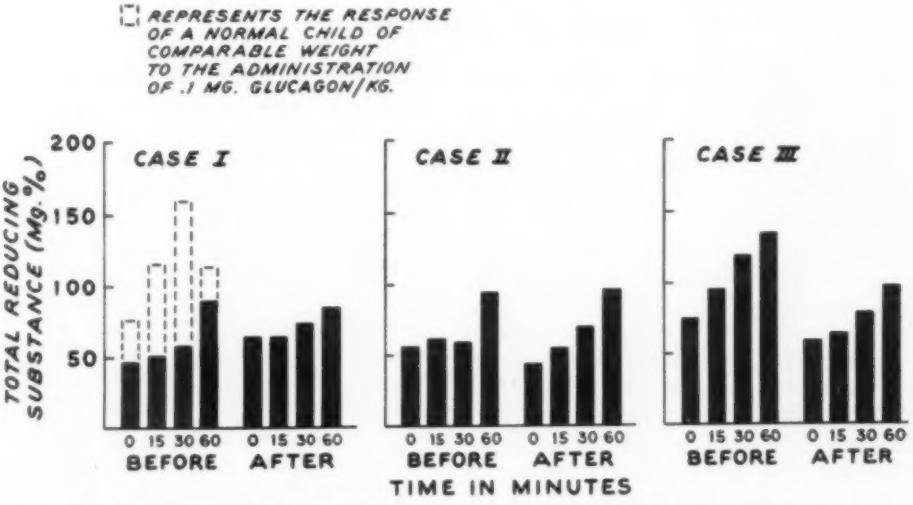

Fig. 11.—Glucagon tolerance test before and after sodium *l*-thyroxine therapy, showing a consistent refractoriness to glucagon.

produce an increase in blood sugar concentration. The response was slower to develop and significantly less than in normals. The maximum increase did not occur until 60 minutes after glucagon administration and ranged from 38 to 61 mg. per 100 cc. A normal child's response to considerably less hormone is included for comparison (Fig. 11).

The relative lack of response to one injection of glucagon or epinephrine was to be expected, since the defect is in the enzyme glucose-6-phosphatase. Despite this, the effect of repeated administration of glucagon was considered to be of interest. Prior to sodium *l*-thyroxine therapy in Case 3, we could find no effect on fasting blood sugar or on the response to one injection of glucagon following its around-the-clock administration for one week (0.3 mg. per kilogram of body weight per 24 hours in four divided doses).

Case 1 and Case 2 were studied similarly. These studies, however, were conducted during the seventh week of sodium *l*-thyroxine therapy. Following the week of glucagon administration, a single dose caused a greater rise in blood sugar (Fig. 12).

An increase in liver glycogen has been observed in rats and rabbits following chronic administration of glucagon.[26] This is of interest, since an effective increase of active liver phosphorylase favors glycolysis rather than glycogenesis. Chronic glucagon administration may have resulted in an increase in glycogen stores which were more available for action of phosphorylase.

Sodium *l*-thyroxine has been used in these children with the assumption that it may exert an action on glucose-6-phosphatase, an action disassociated from its more classical primary effect on tissue respiration. This assumption has been based, in part, upon the known relationship between thyroxine and bone growth and maturation and the relationship of glycolysis to the latter,‡ as well as upon the fact that excess thyroxine leads to depletion of liver, kidney, and cardiac muscle glycogen stores, as mentioned in the discussion of Dr. Russell's paper presented before a Ciba Foundation Colloquoia on Endocrinology.[29]

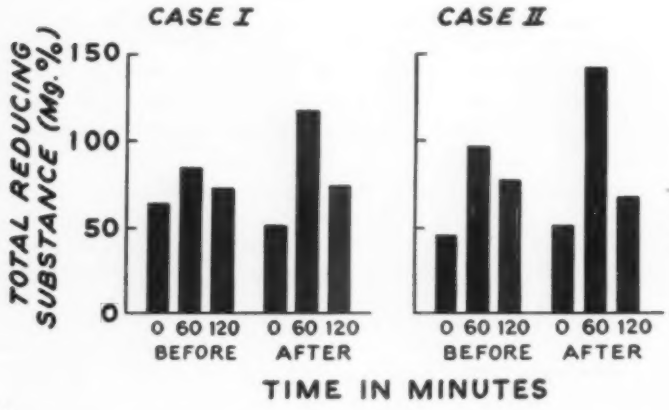

Fig. 12.—Glucagon tolerance test before and after one week on glucagon therapy (I. M.) after six weeks of sodium *l*-thyroxine therapy.

If the effect of sodium *l*-thyroxine in these children had been one only of increasing their energy expenditure, the metabolic manifestations of the disease would have been theoretically exaggerated, i. e., they would have shown an even greater tendency to hypoglycemia and ketogenesis with fasting, a greater sensitivity to insulin, and a reduced response to glucagon and epinephrine administration. This did not occur. Rather, data have been presented suggesting that sodium *l*-thyroxine has exerted some effect on glucose-6-phosphatase. This is not to say

‡ References 27 and 28.

that energy expenditure has not also been increased.

The reduction in concentration of blood nonfermentable reducing substance with sodium *l*-thyroxine administration is also of interest. If the abnormally high concentration of these substances was secondary to their accumulation in the liver due to reduced phosphatase activity and if sodium *l*-thyroxine released this block by effecting an increase in phosphatase activity, this result would be expected.

While these three children did not demonstrate signs suggesting clinical hypothyroidism, it is of interest that the oldest (Case 1) had a decided deficit in linear bone growth and that her skeletal age was retarded by one and one-half years. The dosage of sodium *l*-thyroxine in each case was selected to provide a serum hormonal iodine concentration greater than 8γ per 100 cc.[20] No toxicity was manifest.

Our experience corroborates the observation of other workers that there is decided value in the use of a high-protein diet and frequent feedings.§ We would add that, optimally, the diet should be galactose-free. While the addition of rather large doses of sodium *l*-thyroxine appears to have been of benefit in these three cases, delineation of its ultimate role in the management of classical von Gierke's disease must obviously await more extensive clinical trial and experimental justification.

SUMMARY

Three cases of classical (hepatic) von Gierke's disease are presented, together with data from selected metabolic studies conducted before and after a six-week course of sodium *l*-thyroxine. A high protein, galactose-free diet is outlined and has been found to be of value in the management of this disorder.

Marked insulin sensitivity and relative unresponsiveness to the administration of epinephrine and glucagon was demonstrated in these cases.

Analyses of fasting blood specimens revealed that a large per cent of their total reducing substance was nonfermentable and also showed their tendency to hypoglycemia.

Sodium *l*-thyroxine administration for six weeks was associated with a significant disappearance of the nonfermentable reducing substance in blood with a corresponding increase in fermentable reducing substance. Moreover, sensitivity to insulin was reduced. A one-week course of glucagon administration during sodium *l*-thyroxine therapy was followed by an exaggerated short-term response to that substance.

Dr. Jackson Crane, Assistant Professor of Pathology, Pediatrics, and Surgery, University of California Medical Center, helped in this study.

§ References 9 and 16.

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Pregnancy Experience and the Development of Childhood Speech Disorders

An Epidemiologic Study of the Association with Maternal and Fetal Factors

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Injury to the brain as a cause of neurologic and behavioral dysfunction has been described for centuries. It has been known for a long time that cerebral damage following complications of pregnancy and prematurity is an important factor in fetal and neonatal mortality. We therefore hypothesized that varying degrees of brain injury insufficient to cause death would result in corresponding degrees of neurologic impairment and would serve as precursors to a number of neuropsychiatric disorders of childhood.[1] We have investigated this hypothesis of a continuum of reproductive casualty and found it to have validity as far as cerebral palsy,[2] epilepsy,* mental deficiency,† and childhood behavior disorders are concerned.‡

A number of observations led us to believe that speech disorders might be a component of this continuum. Specific injury to the brain in adults has been reported as resulting in speech defects. Disorders of speech are very common among children with cerebral palsy and mental deficiency. Clinical impressions have indicated that speech disorders were commoner among boys than among girls. This phenomenon has been observed among other neuropsychiatric disorders, including those we had previously investigated, where brain injury was suspected of playing some role.

In 1951, Boland [10] reported that instrumental deliveries were more frequent in a group of 209 stutterers born between 1940 and 1949. Owing to the absence of a control group he was forced to compare his results with reports in the literature based on data on deliveries before 1940, when forceps were not used quite so frequently as after 1940. In addition, since he used information supplied by the mothers of the stutterers, he had to assume "that one-third of mothers whose children were delivered with instruments will fail to report that fact 21 months or more after the birth." Boland did not differentiate among low-, mid-, and high-forceps deliveries, and it is now fairly well-accepted obstetric practice to use low forceps, by far the commonest use of instruments, to avoid injury to the fetus. Boland also reported that

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Professor of Psychiatry, The Ohio State University College of Medicine and Director of Research, Columbus State Psychiatric Institute (Dr. Pasamanick). Formerly Research Assistant, Division of Mental Hygiene, The John Hopkins University School of Hygiene and Public Health (Mrs. Constantinou). Chief, Department of Statistics and Epidemiological Research, Roswell Park Memorial Institute, Buffalo (Dr. Lilienfeld).

* References 3 and 4.
† References 5 and 6.
‡ References 7-9.

there was no significant difference as far as incidence of prematurity was concerned.

It seemed that this problem could be more adequately approached by selecting a group of children with speech defects and reviewing their mothers' obstetrical records and their birth certificates with regard to the presence of certain maternal and fetal factors. The results could be compared with those from an adequately selected control group of birth records. This is a report of the results of such an investigation.

METHOD OF STUDY

The records of all the white children born since 1940 who did not have cerebral palsy or mental deficiency and were receiving speech therapy in the Division of Special Education of the Baltimore Department of Education were searched for names, identifying information, type of speech disorder, suspected etiology, and intelligence quotient. Nonwhites were not included in this analysis because of the possibility that sociocultural factors among Negroes would tend to dilute causation heavily and to conceal any organic factors which might be present.[11] Although it was ascertained that a large number of Negro children were receiving speech therapy because of incomprehensible dialects, it was not believed that their heavy Southern dialect could be attributed to brain injury.

The birth register maintained by the Bureau of Vital Records of the Baltimore City Health Department was then searched for the birth certificates of these children. As a control series of births with which the speech disorder cases could be compared, the next birth reported from the same place of birth as the speech case, matched by race and maternal age groups, was selected. The maternal age groups used were the following: under 20, 20 to 24, 25 to 29, 30 to 34, 35 and over. If the matched control had died during the neonatal period as determined either from the birth certificate or from the hospital record, this birth was omitted from the control series and the next birth with the characteristics noted above was selected. This was done because there was no chance that speech disorder would manifest itself in a child dying during the neonatal period. Such a child should not, therefore, be considered as a control whose prenatal and paranatal experiences could be compared with those of a child who had survived the neonatal period and later developed a speech defect. From the birth certificate the following information was obtained on each speech case and its matched control: place of birth, maternal age, total number of previous pregnancies, number of previous infants born alive and now living, number born alive and now dead, and number born dead.

In those instances where the speech-defective child and its matched control were born in a hospital, the following information concerning the pregnancy and delivery was abstracted from the hospital record: total number of previous pregnancies of the mothers, numbers of previous abortions, previous stillbirths, previous premature births, previous neonatal deaths, length of labor, complications of pregnancy and labor, operative procedures, birth weight, and condition of the child during the neonatal period. The person obtaining this information from the hospital record was not informed whether the birth was that of a speech case or a control child. The hospital records did not contain information concerning the abnormalities studied on a small number of both cases and controls. The size of these groups differed depending on the specific abnormality, resulting in some variation in the totals presented in this report.

Birth certificates were located for 424 children with speech disorders. The clinical types of speech disorders as recorded by the therapists and the number of children with these types were as follows: articulation 291; stuttering 102; voice 31; other types 12; type not stated 6. A few had multiple diagnoses. The etiological classification with the number of children in each category was as follows: functional 195; psychological 89; structural 12; other causes 2; cause not stated 126. Of these 424 children, 290, or 68.4%, were born in hospitals, thereby reducing to this number those cases upon whom information concerning complications of pregnancy, prematurity, and delivery was available.

One might question the reliability of inferences drawn from cases of speech disorder that were obtained from a public school population and that consequently might be expected to have an overrepresentation of persons in lower income groups. It was possible to examine this point by utilizing census-tract information which permitted the grouping of the cases into various economic categories. The children with speech disorders and their matched controls were essentially similar with respect to their socioeconomic status.

RESULTS

Among both cases and controls, approximately 52% were male. It is of interest that 18 children with speech disorders, representing 4.2% of the cases, were the results of multiple pregnancies. This is statistically significantly higher ($P<0.01$) than among the control group (1.2%) and in the general

TABLE 1.—*Specific Complications of Pregnancy Among Mothers of Children with Speech Disorders and Mothers of Their Matched Controls*

Maternal Complication	Cases	Controls
Toxemias of pregnancy	20	18
Bleeding during pregnancy and labor (cause not specified)	5	4
Nonpuerperal complications*	16	8
Breech presentation	12	2
Dystocia owing to abnormal pelvis	6	7
Miscellaneous puerperal complications†	3	2
Premature separation of placenta	1	2
Dystocia other than due to abnormal pelvis	8	22
Placenta praevia	2	1
Prolapse of cord	0	1
Malpresentation other than breech	7	6
Number of individuals on whom information was available	272	282

* Nonpuerperal complications include diseases associated with but not related to pregnancy.
† Miscellaneous puerperal complications include pyelitis, other genitourinary diseases, and hydramnios.

population (1.2%).§ The remainder of the findings will be concerned with the single-birth group, since the number of multiple births is relatively small.

A comparison of the distribution of the various complications of pregnancy and parturition that had occurred among mothers of the speech-defective children and the matched controls is presented in Table 1. In view of the fact that many mothers have more than one complication, a frequency distribution of children according to the number of maternal complications is presented for these groups in Table 2. From these comparisons we note that for the speech disorder cases the percentage of mothers with one or more complications is 25.0, as compared to 18.4 for the control children, a difference that is not statistically significant. There also appears to be no significant difference between cases and controls with regard to exposure to multiple complications, 5.5% of cases as against 3.6% of controls.

§ In this report differences are considered statistically significant if they reach a probability level of 0.05 or less.

TABLE 2.—*Frequency of Complications of Pregnancy Among Mothers of Children with Speech Disorders and Among Mothers of Their Matched Controls*

No. of Maternal Complications	Cases		Controls	
	No.	Per Cent	No.	Per Cent
0	204	75.0	230	81.6
1	53	19.5	42	14.9
2	14	5.1	9	3.2
3	1	0.4	1	0.4
Total	272	100.0	282	100.0
No. having 1 or more complications	68	25.0	52	18.4
No. having 2 or more complications	15	5.5	10	3.6

In view of the previously observed relationships of prematurity with the other neuropsychiatric disorders studied and because of the clinical observations that premature infants are more susceptible to anoxia, a comparison of the prevalence of prematurity among the cases of speech disorder with the controls was made. There was less prematurity among the cases (4.7%) than among the controls (8.0%), although this difference was not significant.

From the hospital records information was obtained concerning the status of the infant during the neonatal period. Infant abnormalities that were considered were convulsions, cyanosis, and asphyxia. Corroboration of the clinical impressions was obtained by information concerning the need for oxygen. It is generally accepted that such conditions are under-reported on the hospital record, except for the severer forms. Again there was no significant difference between cases (9.0%) and controls (10.6%).

In view of the fact that these neonatal abnormalities and prematurity are both associated with each other as well with maternal complications, we thought it desirable to summarize the prenatal and paranatal factors presented by disregarding the overlapping that occurs between these conditions. Thus, we would consider only those children who were exposed to one or more complications, prematurity without maternal complications, and neonatal abnormalities without either maternal complications or prematurity. We would then obtain an estimate of the total frequency of abnormal prenatal and paranatal factors in each of our groups. Such a compilation is presented in Table 3. In our speech-disorder group 29.8% have been exposed to one or more of these abnor-

TABLE 3.—*Frequency of Various Abnormalities of Prenatal and Paranatal Periods Among Speech-Disorder and Control Births*

	Cases		Controls	
	No.	Per Cent	No.	Per Cent
Total with one or more maternal complications of pregnancy	68	25.0	52	18.4
Total premature births without maternal complications	5	1.8	12	4.3
Total with abnormal conditions during neonatal period without prematurity or maternal complications	8	2.9	12	4.3
Total with abnormalities of prenatal and paranatal periods	81	29.8	74	26.2
Total number of children	272	....	282	....

TABLE 4.—*History of Previous Infant Loss Among Mothers of Children with Speech Disorders and Among Mothers of Their Matched Controls* *

Birth Order		Total No. of Mothers	History of 1 or More Previous Infant Losses*	
			No.	Per Cent
2	Cases	105	7	6.7
	Controls	96	16	16.7
3 and 4	Cases	97	17	17.5
	Controls	75	16	21.3
5 or more	Cases	49	25	51.0
	Controls	51	28	54.9

* A mother was considered to have had a previous infant loss if she reported on the birth certificate that she had had either a previous live birth that was now dead or a previous stillbirth.

malities, as contrasted to 26.2% of the controls, a statistically nonsignificant difference.

It was possible to compare the group of speech-disorder children with the controls with regard to duration of labor and the types of operative procedures performed at time of delivery of these children. No essential differences were noted.

In our other studies we had noted that previous reproductive casualties were more frequent among mothers of children with those neuropsychiatric disorders found to be associated with complications of pregnancy and prematurity.[12] We were therefore interested in comparing the history of previous infant loss among mothers of the speech-disorder cases with the control group. Table 4 indicates that, if anything, the mothers of the controls had a greater previous infant loss than the cases, although the difference was not statistically significant (P=0.08) as determined by a method of analysis described by Cochran.[13]

Glasner has reported that 45% of stutterers were only children.[14] This is approximately the proportion found in the general population. We were interested in examining this relationship, since it might throw some light upon etiology. Our results are presented in Table 5 in terms of a comparison of observed and expected numbers. These expected numbers were computed from the maternal-age-birth-order distribution of all the births occurring in Baltimore during the same period of time as the cases. We note that, contrary to the previous report, speech disorders occur oftener among children of the higher birth ranks, that is, in the third, fourth, and fifth or later-born children. This relationship is highly significant statistically ($P<0.01$). It also appears that there is no significant relationship with maternal age.

COMMENT

It seems rather obvious that, when speech disorders not associated with cerebral palsy

TABLE 5.—*A Comparison of the Observed and Expected Maternal-Age-Birth-Order Distribution of Children with Speech Disorders* *

Maternal Age	Number of Previous Pregnancies													
	0		1		2		3		4		5 or More		Total	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
Under 20	24	27.1	6	4.6	2	0.7	..	....	..	....	..	....	32	32.4
20-24	38	71.2	42	33.5	16	10.3	16	3.1	3	1.0	0	0.3	116	119.4
25-29	24	39.8	35	37.1	20	16.1	9	6.9	7	2.5	7	2.5	102	105.5
30-34	9	15.0	18	19.8	9	12.5	9	6.0	3	3.1	9	4.7	57	61.1
35 and over	5	5.2	3	7.3	8	6.3	8	4.2	2	2.7	18	6.5	44	32.2
Total	100	158.3	105	102.3	55	45.9	42	20.2	15	9.9	34	14.0	351	350.6

* Expected numbers were computed from the maternal-age-birth-order distribution of all single births in Baltimore during the same period of time.

or mental deficiency are considered as a group, there is no association between this neuropsychiatric disorder and complications of pregnancy, parturition, and prematurity. In view of the higher percentage of boys found in the other neuropsychiatric disorders, this observation might have been suggested had it been known that there was no greater incidence of speech disorders among boys, as we later found in this study. On the basis of these data it can be inferred that brain injury plays little or no role in the production of speech disorder except in defective or palsied children. This statement requires some qualification, since it is possible that if larger numbers of children with speech disorders were studied, the somewhat higher percentage of cases whose mothers had complications of pregnancy might be found to approach significance. However, in view of the reversal of expected findings with regard to prematurity, neonatal abnormalities, and history of previous infant losses, this appears to be unlikely. It is also possible that if stuttering or articulatory disorders were studied separately in sufficiently large numbers, some association with prenatal and paranatal factors might be found. Since we found no differences in the total group of speech disorders, it seems unlikely that we would find any differences when studied separately.

The finding of a significantly higher proportion of multiple pregnancies among the speech-disorder cases is similar to that found in our studies of the other neuropsychiatric disorders. The possibility of cerebral injury is increased in multiple pregnancies, but in view of the finding of a lack of association between speech disorder and these precursors of injury, it appears reasonable to assume that psychological factors rather than biological ones are involved. It is possible that twins who have more contact with each other than is deemed desirable, rather than with maturer children, have learned from each other immature, faulty, speech patterns which have become more or less fixed due to proximity and mutual comprehension of impaired speech. In addition, the lack of comprehension of their speech by others would in turn tend to make them more dependent upon their own society.

A somewhat similar hypothesis can be postulated for the finding of the occurrence of increased risk of speech disorders in the higher birth orders. Here, too, the rivalries, disorganizations, and frustrations of life in large families may be some of the determining factors in the development of speech disorders in children. The impatience of family members with speech in the younger siblings that is difficult to comprehend and immature may also be sufficient to produce and fix faulty speech behavior. It might also be hypothesized that the busy, impatient mother with a large brood to care for and with little time and attention for each child might also aid in the production of speech disorders.

Our findings would appear to make these hypotheses worthy of further, more definitive, investigation, since the possibility for the prevention of some of these psychologically and socially disabling disorders would lie within the realm of possibility if the etiology could be more definitively fixed upon these psychosocial determinants. Guidance to mothers in the early management of the speech behavior of their children may prove to be an important factor in the prevention and early treatment of speech disorders in children.

SUMMARY

The prenatal and paranatal records of 424 nondefective and nonpalsied children with speech disorders did not show more complications of pregnancy and delivery, prematurity, abnormal neonatal condition, and previous reproductive casualty than the records of a similar number of matched controls. It seems that prenatal and paranatal brain injury may be largely eliminated as an important factor in the etiology of speech disorders in otherwise normal children. The findings of more multiple pregnancies and more later-born children in the speech-defective group suggests the role of psychosocial factors in the etiology of speech disorders. The prevention of some of these psychologically and socially disabling dis-

orders may lie in the guidance of mothers in the early management of speech behavior in their children.

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Infantile Cortical Hyperostosis

Report of Seventeen Cases

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The roentgen finding in young infants of cortical subperiosteal new bone formation, commonly involving the mandible, usually associated with an extremely variable course of fever, swelling, and irritability was identified as a new syndrome almost simultaneously by Caffey * and Smyth [8] about 10 years ago. Probably the first case of this disease was reported some 15 years before the reports of Caffey and Smyth, however, when Roske † described a single case of subperiosteal new bone formation involving the long bones and the mandibles in an infant boy. The syndrome was called infantile cortical hyperostosis by Caffey and was thought to be a benign disease of variable duration.[1] There was no mortality in the first 24 cases reported.[3] Later reports (which now include more than 70 cases) have listed several deaths from intercurrent infections ‡ and several instances of bony deformity.§ The syndrome was for a time confused with vitamin A poisoning.‖ The etiology has not yet been established. Caffey noted a number of similarities between infantile cortical hyperostosis and transmissible osteopetrosis of fowls.¶ Thus far, all cultures and serological tests for an infectious agent have been negative.[19] Bush [16] suggested that the adrenal hormones might have a beneficial effect in infantile cortical hyperostosis similar to that in rheumatoid arthritis. Several cases have been observed at birth,# and a few, even in utero.[17] It has been postulated that a local arterial lesion is the primary cause of the disease.* The familial pattern of incidence † and the average age of onset of 9 weeks [10] are features similar to those of hypertrophic pyloric stenosis.

Sherman and Hellier [19] reviewed a 20-year accumulation of x-ray films and did not find a case of infantile cortical hyperostosis. They suggested that it is either a new disease or an old disease of greatly increased incidence. Sidbury and Sidbury [10] noted 10 cases in four years of private practice and commented that the disease is commoner than is generally appreciated.

In approximately six and a half years, 17 cases of infantile cortical hyperostosis have been seen in this hospital. It is the purpose of this paper to report these cases, to comment on the diseases commonly confused with infantile cortical hyperostosis, and to encourage a high index of suspicion for this disease during the first 6 months of infancy.

REPORT OF CASES

CASE 1.—A 17-week-old white girl was admitted to the hospital on Nov. 10, 1948, because of a persistent swelling of the left face for approximately two weeks and swelling of the right arm for one day. The baby had also had a low-grade fever. She had received a course of penicillin without effect. Physical examination revealed an irritable but well-developed baby. Hard indurated swellings of the right face, left parotid area, and right forearm were noted. None of the swellings were tender. Laboratory studies revealed WBC

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* References 1 and 2.

† Roske, G., cited by Sherman and Hellier.[19]

‡ References 6-8.

§ References 1 and 8-12.

‖ References 4, 13, and 14.

¶ References 4 and 15.

References 10 and 16.

* References 10 and 17.

† References 10 and 18.

Fig. 1.—Facial swelling in a typical case.

count, 24,300; polymorphonuclear cells, 38%; hemoglobin, 12.4 gm.; serological test for syphilis, negative; blood culture and tuberculin skin test, negative. X-ray examination revealed periosteal hyperostosis involving the entire length of the right ulna. The radius was normal. There was also marked periosteal hyperostosis of the mandible. The day after admission, a new swelling was noted on the posterior medial aspect of the right tibia. She remained in the hospital for three days. During this time the swellings subsided slightly. She was completely free of signs or symptoms of the disease six years later, at which time she was admitted to this hospital for a tonsillectomy.

Case 2.—A 16-week-old white boy was admitted to the hospital on March 8, 1949, in order to investigate the etiology of swelling and paralysis of the left arm of a week's duration. Syphilis, fracture, and brachial plexus injury were considered as possible diagnoses. Physical examination revealed a fretful baby who did not move the left arm. The left forearm was swollen, pale, and tender. Laboratory examination revealed WBC count, 11,300; polymorphonuclear cells, 36%; hemoglobin, 10.2 gm.; sedimentation rate, 18 mm. in an hour; serum vitamin A and C levels, normal; serological test for syphilis, negative. X-ray examination revealed extensive periosteal hyperostosis of the ulna and minimal involvement of the left radius. The patient remained in the hospital for five days. During this time the swelling did not change. The swelling subsided three months after discharge from the hospital. At the present time, six years later, this child has no residual signs or symptoms of the disease.

Case 3.—A 7½-week-old Mexican girl was admitted to the hospital on July 18, 1949, because of swelling of the right shoulder blade for the previous two weeks. The admission diagnosis was possible malignant tumor. There was moderate swelling over the right scapula extending into the right axilla. The overlying skin appeared reddened. Laboratory work revealed serological test for syphilis, negative; WBC count, 18,200; polymorphonuclear cells, 43%; hemoglobin, 11 gm. X-ray examination revealed periosteal new bone formation completely surrounding the right scapula and obliterating the normal bony architecture. Roentgen examination of the other bones revealed normal findings. The baby was operated on because it was thought that she possibly had a malignant tumor. Muscle and bone biopsy specimens were taken. The musculature was described as being edematous, fibrotic, and fairly avascular. The bone had a granular appearance. The periosteal surface appeared rough and was relatively avascular. Histologically, there was atrophy, increased fibrous tissue, and edema of the muscles. There was fibrous replacement of the marrow associated with a few infiltrating round cells. Tissue cultures were negative. After surgery the child recovered satisfactorily, but the swelling increased slightly. She was discharged from the hospital nine days after surgery. Five years later there was no clinical evidence of the disease.

Case 4.—An 11-week-old white boy received two blood transfusions on Feb. 17 and Feb. 22, 1950, in the outpatient department because of anemia secondary to Caffey-Smyth disease. The baby had had a low-grade fever and swelling of the jaw for two weeks. No improvement had occurred with penicillin. He was irritable and had bilateral firm parotid swellings. Laboratory work revealed WBC count, 37,600; polymorphonuclear cells, 69%; hemoglobin, 7.5 gm. X-rays revealed extensive hyperostosis of

Fig. 2.—X-rays of case with mild involvement of mandible. Note marked soft tissue swelling.

the mandible, scapulas, and practically all of the long bones, including all of the ribs. Six months later there was expansion of the medullary spaces and thinning of the cortices of both tibias and fibulas. Soft tissue swelling subsided after seven months. Four years later there was no deformity.

CASE 5.—A 30-week-old white boy was admitted to the hospital on May 5, 1950, because of fever, refusal to move the right arm, and swelling of the right cheek for one day. The admission diagnosis was fever of undetermined etiology. At the time of admission, the temperature was 102 F. The temperature remained elevated for four days. He was an irritable baby with a slightly swollen right arm. The right arm was slightly warmer than the left and had a reddish area above the elbow. Laboratory examination revealed WBC count, 15,200; polymorphonuclear cells, 57%; hemoglobin, 14.4 gm.; sedimentation rate, 40 mm. in an hour. X-ray examination revealed periosteal hyperostosis of both humeri. The baby received penicillin for a few days, with no apparent improvement. He remained in the hospital for a total of six days. The swelling of the right arm subsided approximately four weeks after his discharge from the hospital.

CASE 6.—A 10-week-old white girl was admitted to the hospital on May 6, 1950, because of anemia secondary to Caffey-Smyth disease. Physical examination revealed firm nontender swellings of the cheeks and jaws. Laboratory examination revealed WBC count, 24,000; polymorphonuclear cells, 70%; hemoglobin, 9.4 gm. X-rays revealed periosteal hyperostosis of the mandible. The baby received two small blood transfusions while in the hospital. The swellings remained unchanged during her three-day hospitalization. She had progression of the disease to almost all the long bones a short time after her hospital discharge.

CASE 7.—A 13-week-old white girl was admitted to the hospital Feb. 17, 1951, because of swelling of the jaw for one week. The admission diagnosis was suspected Caffey-Smyth disease. She had had a low-grade fever for 10 days. There were tender swellings over both sides of the mandibles. Laboratory studies revealed serological test for syphilis, negative; WBC count, 18,700; polymorphonuclear cells, 27%; hemoglobin, 9 gm.; serum calcium, phosphorus, and alkaline phosphatase, normal. X-ray examination revealed periosteal hyperostosis of the left humerus and of the mandible. Three weeks later, x-ray revealed hyperostosis of both clavicles, all the long bones, and the left ribs. There was no clinical evidence of involvement of these bones. While in the hospital, the child received three small blood transfusions. The swelling of the jaws subsided only slightly during her 19-day stay in the hospital. After the patient's discharge from the hospital, the swelling gradually disappeared during the next two months. One year later, there was no x-ray evidence of the disease.

CASE 8.—An 11-week-old white boy was admitted to the hospital on Nov. 23, 1951, because of a swollen jaw for one month and fever for three days. Physical examination revealed a very irritable baby. There were hard swellings over both jaws and both clavicles. No redness or increased warmth was noted. Laboratory studies revealed WBC count, 36,000; polymorphonuclear cells, 35%, and hemoglobin, 8.5 gm. X-ray examination revealed periosteal hyperostosis of both mandibles, the ribs, the clavicles, and the arm bones. During the baby's 3-day stay in the hospital the swellings remained unchanged. The child received one small blood transfusion in the clinic three days after discharge from the hospital. The baby had a very stormy course. Soft tissue swellings subsided and recurred periodically until he was 11 months old. At the age of 11 months, he was quite small, weighing only 15 lb. X-ray examination three years later revealed no evidence of the disease.

CASE 9.—An 18-week-old Mexican girl was seen in the clinic on April 24, 1952, because of intermittent facial swelling for one month. The initial

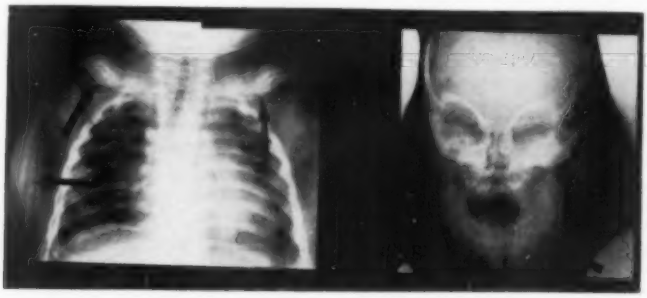

Fig. 3.—X-rays showing extensive involvement of mandible, clavicles, and humerus.

diagnosis was possible Caffey-Smyth disease. The temperature was normal. Physical examination revealed an irritable baby with firm swellings of both sides of the jaw, which were not red or warm. Laboratory examination revealed a hemoglobin of 11.2 gm. X-ray examination revealed periosteal hyperostosis of the mandible bilaterally. This patient did not return for follow-up examination.

CASE 10.—A 19-week-old Negro boy was admitted to the hospital on Nov. 19, 1952, in order to have an inguinal hernioplasty. Other than the hernia, there were no specific complaints. Pediatric consultation was obtained when a routine WBC count was found to be 27,000, with 42% polymorphonuclear cells. The hemoglobin was 9 gm. No explanation for this elevation of the white cell count was apparent on physical examination. A chest film taken at this time to rule out the possibility of pneumonia revealed periosteal hyperostosis of the clavicles, the humeri, the ulnas, the mandible, and the right sixth rib. The temperature was normal. The serological test for syphilis was negative. A sickle-cell preparation was negative. The patient was given a transfusion. Five days after admission he received penicillin for a few days because of pharyngitis associated with a low-grade fever. The inguinal hernioplasty was performed approximately two weeks after admission. The patient developed a wound infection 10 days after surgery. The baby remained in the hospital for approximately one month. One month after the original diagnosis was made, x-ray examination revealed extension of the disease to the legs and ribs. Seven months later, x-ray examination revealed only minimal hyperostosis of the mandible and femurs.

CASE 11.—A 21-week-old white girl, a fraternal twin, had x-rays taken at this hospital on Sept. 30, 1953, because of increasing swelling of the left face for two weeks. The initial diagnosis was possible parotid tumor. Laboratory findings revealed WBC count, 16,700; stab cells, 5%; hemoglobin, 9.5 gm. X-ray examination revealed periosteal hyperostosis of the mandible bilaterally, with the greatest reaction on the left side. The clavicles appeared normal. The patient was cared for at home and improved rapidly.

CASE 12.—An 18-week-old white boy was admitted to the hospital on July 11, 1954, because of swelling about the face for three and one-half weeks. A diagnosis of mumps had been made initially, but this diagnosis was later changed to cellulitis of the face which was resistant to penicillin. The child had had a low-grade fever for two weeks. The temperature was 101 F on admission. Physical examination revealed an irritable child. There was a firm swelling of the left cheek from the maxilla to the angle of the mandible. There was no redness or increased warmth of the overlying skin. The mucous membranes of the left side of the mouth were swollen. The orifice of Stenson's duct was normal. Submaxillary nodes were palpable. Laboratory examination revealed serological test for syphilis, negative; WBC count, 27,350; polymorphonuclear cells, 34%. X-ray examination revealed periosteal hyperostosis of the mandible bilaterally and hyperostosis of both fibulas. The heterophile test was negative. The baby's facial swelling subsided slightly during his six-day hospital stay. Clinical and roentgen follow-up were not obtained.

CASE 13.—A 23-week-old Negro girl was seen at our clinic on Sept. 2, 1954, because of swelling of the right cheek for one day. There had been intermittent swelling of the eyes for a number of weeks. Suggested diagnoses had included tear duct obstruction, infection, and trauma. Physical examination revealed swelling of the lower eyelids and swelling of the right cheek. The swellings were tender, but redness and increased warmth were not noted. X-ray examination revealed periosteal hyperostosis of the right side of the mandible. There was no hyperostosis of the facial bones or skull. The swelling of the right jaw persisted for four weeks. X-ray examination eight months after the onset of symptoms showed no abnormality.

CASE 14.—A 13-week-old white girl had x-rays taken at the hospital on Oct. 20, 1954, because of limpness of the right arm of one week's duration. Physical examination revealed that motion of the right shoulder was painful. The right arm was noted to be rather flaccid. No swelling was noted. X-ray examination revealed periosteal hyperostosis along the lateral border of the right scapula. No other x-ray changes were noted. The patient did not return for follow-up examination.

CASE 15.—An 18-week-old Negro girl was seen at our clinic on Jan. 28, 1955, because of swelling of the right jaw for three days. She was afebrile. Physical examination revealed a very irritable baby with a firm diffuse tender swelling of the right mandible. There was no redness. There were palpable anterior cervical lymph nodes. Laboratory examinations revealed WBC count, 17,550; polymorphonuclear cells, 38%; hemoglobin, 10.6 gm.; serum calcium, phosphorus, and alkaline phosphatase, normal. X-ray examination revealed periosteal hyperostosis along both borders of the mandible. X-rays of the clavicles, ribs, and humeri were negative. The swelling persisted for approximately five days. The patient did not return for follow-up examination.

CASE 16.—An 18-week-old Negro girl was seen in the clinic on April 18, 1955, because of persistent swelling of the jaws and a low-grade fever of three weeks' duration. She had been treated with penicil-

lin for two weeks, with a diagnosis of cellulitis of the face. Physical examination revealed a very irritable baby with marked jaw swelling which was tender but not red or warm. There was an eczematoid rash on the cheeks and a small umbilical hernia. Laboratory examination revealed WBC count, 24,300; polymorphonuclear cells, 44%; hemoglobin, 6.6 gm.; serological test for syphilis, negative; tuberculin skin test, negative; alkaline phosphatase, normal. X-ray examination revealed bilateral mandibular periosteal hyperostosis. This baby is presently under observation.

CASE 17.—A 12-week-old Portuguese girl was admitted to the hospital on April 18, 1955, because of swelling about the right eye and jaw for two weeks. The admission diagnosis was tumor of the face. She had had fever of 101 F on one occasion. The baby had had a moderately severe upper respiratory infection at age 2 weeks and had had a mild cold one week before the onset of the facial swellings. Physical examination revealed an irritable baby with a tender indurated area over the right jaw. There was no redness or warmth. Laboratory examination revealed WBC count, 25,500; polymorphonuclear cells, 33%; hemoglobin, 11.9 gm.; alkaline phosphatase, 6.0 units; tuberculin skin test, negative, and serological test for syphilis, negative. X-rays revealed a line of periosteal hyperostosis along the right mandible. The swelling subsided only slightly during her two-week stay in the hospital. She is now being followed by her private physician.

COMMENT

Eleven of this series of seventeen cases were private patients of staff physicians. The last five cases reported occurred within the past eight months. Seventy-one per cent of the cases were in girls. The disease was observed in Caucasians, Negroes, Mexicans, and in one patient of Portuguese descent. The average age of onset was 14 weeks (range, 4 to 30). There was an average period of two weeks between the onset of symptoms and the establishment of the diagnosis of infantile cortical hyperostosis. Approximately 70% of the cases presented a chief complaint of swellings about the face. Among the many initial diagnoses entertained were idiopathic parotid swelling, syphilis, undisplaced fracture, brachial plexus injury, malignant bone tumor, blocked tear duct, parotid tumor, mumps, cellulitis of the face, paralysis of the arm, and trauma. Sixty per cent had low-grade fever. Tender swellings were almost always found. Warmth and redness of the skin or enlarged lymph nodes were rare. Irritability was frequent. The average white blood cell count was 23,000 (range, 11,300 to 37,600). The average per cent of polymorphonuclear cells was 44%, with a range of 27% to 70%. A moderate degree of anemia was occasionally present. Serological tests for syphilis, cultures, tuberculin skin tests, blood chemistry studies, serological tests for virus diseases, sickle-cell tests, and bone marrow aspirations were negative on the occasions on which they were performed.

The incidence of involvement of the various bones in our cases is as follows: mandible, 76%; humerus, 35%; ulna, 35%; clavicle, 30%; ribs, 30%; radius, 24%; tibia, 24%; femur, 18%; scapula, 18%; fibula, 18%.

In six cases only the mandible was affected. In two cases the scapula was involved as an isolated bone. Clinical swelling in our series was always accompanied by x-ray changes. Minimal mandibular changes often were apparent only on the oblique lateral projection.

Five cases received blood transfusions. All other cases received only general supportive and symptomatic therapy. Case 3 had a biopsy of the scapula. Cases 9, 12, and 16 had received an initial D. P. T. inoculation just a few days after the onset of symptoms. Many others had never had a D. P. T. inoculation. In those cases in which adequate follow-up was obtained, symptoms persisted for as long as 10 months and as short a time as 1 week. Case 4 was the only patient who developed the changes of chronic infantile hyperostosis as described by Caffey.[9] These changes, however, had entirely disappeared when x-rays were made four years later. As far as is known, no permanent deformity occurred in any case.

GENERAL COMMENT

Swelling of the jaw and face due to infantile cortical hyperostosis can be confused with parotitis (Cases 1, 4, 12), parotid tumor

(Case 11), orbital tumor, syphilis [20] (Case 2), facial trauma (Case 13), lacrimal duct obstruction (Case 13), facial cellulitis (Cases 12, 13, 16), scurvy,[3] osteomyelitis, tuberculosis, Ludwig's angina,[21] and familial fibrous swelling of the jaw.[22] Differentiation would be based on x-ray findings of periosteal new bone formation along the mandible associated with the findings of onset during the first six months of life, adequate vitamin intake, no known history of trauma, absence of redness of the skin, no local adenopathy, negative serological test for syphilis, and negative tuberculin skin test. Familial fibrous swelling of the jaw is associated with x-ray evidence of bony changes about the teeth and no evidence of periosteal hyperostosis.[22] Scurvy rarely involves the mandible, almost never occurs under the age of 6 months, and is not confined to the shaft of the bone.[4] In our cases of infantile cortical hyperostosis, clinical swelling was always accompanied by x-ray changes. This stands in sharp contrast to our experience with osteomyelitis. In our cases of osteomyelitis, x-ray changes were usually not apparent until 7 to 14 days after the onset of clinical swelling.

When mandibular changes are not present, one would have to consider, in the differential diagnosis, such entities as brachial plexus injury (Case 2), osseous tumor (Case 3), fracture (Case 2), pleural effusion,[1] rheumatic fever,[2] rheumatoid arthritis,[2] meningitis,[10] vitamin-A poisoning,[13] sickle-cell anemia,[22] Engelmann's disease,[4] poliomyelitis, leukemia, rickets, allergy, feeding problem,[8] anemia, and sepsis.

These diseases can usually be quickly and easily eliminated by history, physical examination, laboratory tests, and x-ray studies. Vitamin-A poisoning is unknown before the age of 6 months and never has been known to involve the mandible. It is always associated with an increased serum vitamin-A level.[13]

Infantile cortical hyperostosis is probably a fairly common disease and should be thought of as a possible cause of any firm tender swelling of the face which occurs during the first 6 months of life. Case 10 illustrates the occurrence of the disease in a patient who was essentially asymptomatic. In Cases 3 and 14 the pathology was confined to the right scapula. We have seen a relatively high incidence of the disease in the past six and one-half years, 17 cases occurring from a group of approximately 6000 hospital- and clinic-registered infants between the ages of birth and 6 months.

SUMMARY

A series of 17 cases of infantile cortical hyperostosis is reported.

Infantile cortical hyperostosis can be confused with a vast variety of diseases. It should be thought of as a possible diagnosis for any firm tender swelling of the face which occurs during the first 6 months of life.

The diagnosis of infantile cortical hyperostosis is readily made by a correlation of the clinical, laboratory, and roentgen findings. The roentgen finding of subperiosteal new bone formation is a nonspecific change, but when it involves the mandible of a young infant it is almost always due to infantile cortical hyperostosis.

In this series clinical swelling was always accompanied by x-ray changes. Oblique lateral projection films were important in the demonstration of minimal mandibular changes.

The etiology of infantile cortical hyperostosis is unknown. There is at present no established specific therapy. The course is usually benign and self-limited.

At this hospital the incidence of this disease is about 3 cases per 1000 hospital- and clinic-registered infants, age birth to 6 months.

5105 Dover St.

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The Failure of Hydrocortisone to Affect Neonatal Jaundice

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There are several known results of cortisone administration which could be beneficial to patients with erythroblastosis fetalis. These include a lowering of serum bilirubin, an amelioration of hemolysis in acquired hemolytic anemia, and a stimulation of erythropoiesis. For these reasons, and because some reports have suggested that it is a valuable adjunct in the treatment of hemolytic disease of the newborn, its use was evaluated in various types of jaundice occurring during the neonatal period.

METHODS AND MATERIAL

The serum bilirubin was measured by a modification of the method of Malloy and Evelyn,[1] with the Coleman Junior spectrophotometer. In most cases, 0.3 ml. of serum was used and observations were made with a microadapter on final volumes of 1.5 ml. at 1 minute and 3.0 ml. at 30 minutes. Rarely, only 0.1 ml. of serum was available and a similar technique was used with greater dilution of the sample. The correction factor was calculated by correlation with the macromethod.

Peripheral blood studies were carried out as previously described.[2] Bone marrow samples were aspirated from the tibia and smeared directly on cover slips. Four hundred cells of each marrow sample were counted.

Only those infants in whom there was evidence of erythroblastosis fetalis or in whom jaundice was observed were included in this study. This material included 102 infants, of whom 38 were premature babies as defined by a birth weight of 5 lb. 8 oz. or less.

The cases with erythroblastosis fetalis were due either to anti-D or anti-A. In either case only those patients with evidence of actual hemolytic disease were included. The remaining cases were classified as physiological jaundice, except for two with hepatitis of an "inspissated bile" pattern.

The patients received cortisone by random selection, while replacement therapy was reserved for cases where past history of kernicterus in the family, prematurity, and/or bilirubinemia indicated it.

RESULTS

The serum bilirubin levels were observed in 56 infants during the neonatal course of physiological jaundice. Studies were done on both premature and full-term babies, but in neither group was any consistent effect of cortisone therapy apparent.

In Figure 1 the serum bilirubin of the premature infants is plotted according to age and the values during hydrocortisone therapy compared to those observed prior to treatment and in 20 untreated controls. The 12 treated infants received a course of therapy usually beginning on the second day but varying up to the eighth day, depending on the time when the infant was first studied. In this group, the course of therapy consisted of 50 mg. of hydrocortisone stat., followed by 20 mg. b. i. d., 15 mg. b. i. d., 10 mg. b. i. d., 5 mg. b. i. d.×2 on succeeding days. No significant difference is apparent between the treated and untreated cases. To avoid

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Director, Rh Laboratory, and Assistant Director, First and Third Medical Services (Tufts), Boston City Hospital; Assistant Professor of Medicine, Tufts Medical School (Dr. Desforges). Resident, Rh Laboratory, Boston City Hospital (Dr. Villadolid).

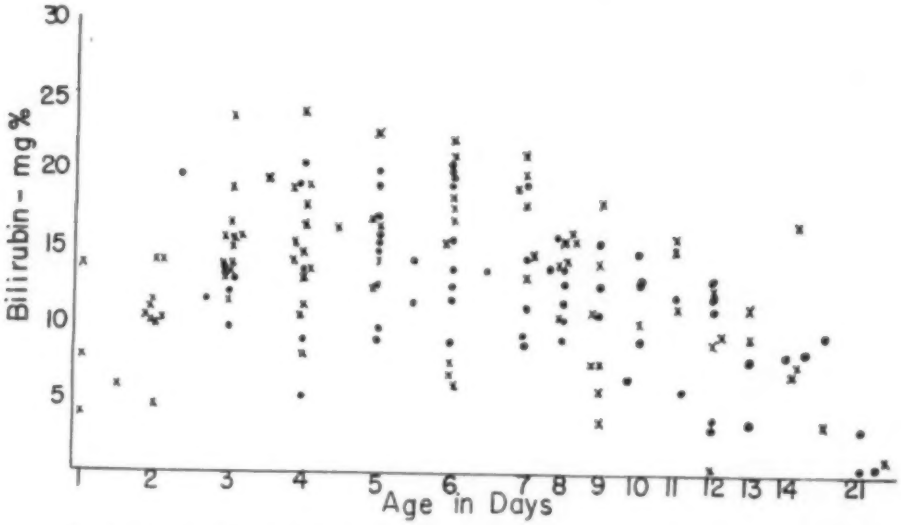

Fig. 1.—The total serum bilirubin values are plotted according to age. The crosses represent those in infants without prior hydrocortisone therapy, and the closed circles indicate values observed after the institution of treatment.

possible influence of more frequent determinations in some infants, the values of each case are plotted as the percentage increment or decrement of the previous value in Figure 2. During the second to fourth days of life in the untreated babies, 8 of 14 samples showed an increase in the bilirubin level, and three of six treated babies had increasing values within this period. From the fifth to seventh days, with more data available, 4 of 15 controls had increasing values, while 7 of 23 determinations in the treated group showed a similar trend. Again, the difference is insignificant.

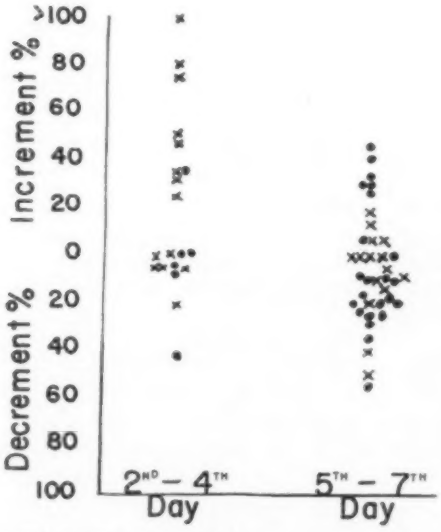

Fig. 2.—The serum bilirubin values are plotted as percentage increment or decrement of the preceding value. The crosses represent the variations observed in untreated babies, and the closed circles indicate those found after the institution of cortisone therapy.

In two patients with hepatitis of inspissated bile pattern following physiological jaundice, one or more trials of hydrocortisone therapy were given and its effect on serum bilirubin observed. In neither case was a definite change brought about in the 1- or 30-minute values which was beyond the limits of the baseline control values.

Patients with erythroblastosis fetalis due either to anti-Rh or anti-A were also included in this study to evaluate the effect of the drug on this disease process. In this group 18 received only replacement therapy and 10 received hydrocortisone alone. Five were given both treatments. The hydrocortisone dosage schedule for 4 patients was 50 mg. stat. on the first day of treatment and 20 mg. b. i. d., 15 mg. b. i. d., 10

mg. b. i. d., 5 mg. b. i. d.×2 on succeeding days. Because of equivocal effects the dosage was increased in 11 cases to 100 to 150 mg. in divided doses on the first day followed by 25 mg. t. i. d., 25 mg. b. i. d., 20 mg. b. i. d., 15 mg. b. i. d., 10 mg. b. i. d., 5 mg. b. i. d.×2 on succeeding days. In the control group the curves had the characteristic early rise with a peak before the third day, but a few did show a second rise or a later peak suggestive of superimposed physiological jaundice. Those patients receiving the hormones had similar curves.

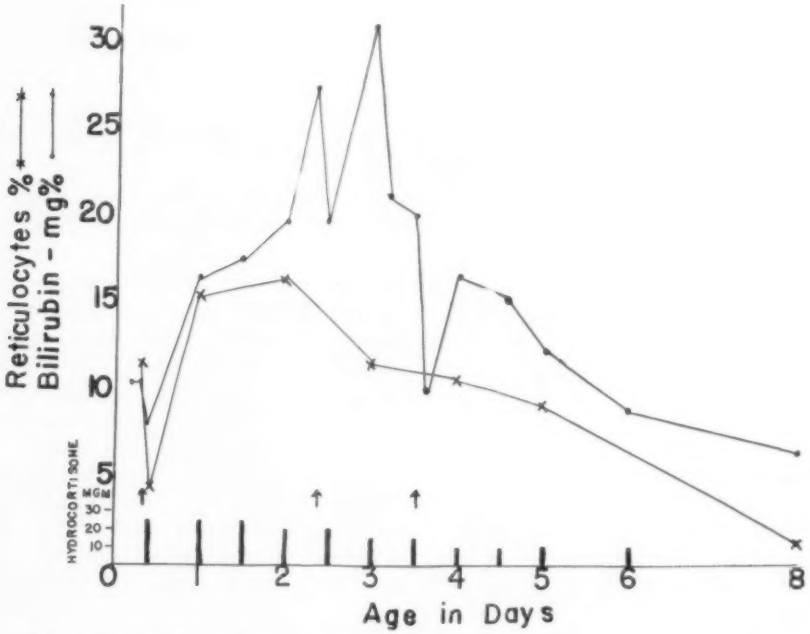

Fig. 3.—The fluctuations in serum bilirubin and percentage of reticulocytes are plotted according to age in an infant with erythroblastosis fetalis who received three replacement transfusions, as indicated by the arrows, during a course of hydrocortisone therapy.

Of those patients started on cortisone therapy, three continued to show bilirubinemia of such a degree that replacement transfusion was given. One case is plotted in Figure 3, in which instance three replacements were carried out during the first 80 hours, when the infant was receiving a total of 145 mg. of hydrocortisone. While occasional patients may have been relieved by the administration of the drug, there was no evident trend in this direction, nor were such cases beyond the known variation of the disease process. In patients receiving replacement therapy, results were similar to those previously reported. In two patients where a second rise occurred after transfusion, the administration of hydrocortisone was followed by a diminution in the values, but the response was gradual and consistent with the course of the disease.

Since cortisone may stimulate erythropoietic activity, reticulocyte levels and marrow cell counts were done in these infants. In neither physiological jaundice nor in hemolytic disease was hydrocortisone found to increase the reticulocyte count or hemoglobin. Since several variables may determine reticulocyte values, marrow aspirations were performed before and a few days after the start of treatment to evaluate erythropoietic activity. The control studies in this series

parallel the findings of Gairdner and others, who reported a rapid decline in erythropoietic cells with a rise in lymphocytic elements beginning 48 hours after birth and lasting three months.[8] In 12 cases, marrow aspirations were studied after the institution of cortisone therapy, and in no case was the decline in the erythroid percentage prevented. It is evident that administration of the hormone did not overcome the diminishing erythropoiesis characteristic of this age group.

In this group of infants, three died, all of them premature babies who received cortisone. The first was a twin who weighed 2 lb. 4 oz. who had physiological jaundice and was given cortisone beginning on the third day of life. He died on the sixth day. Autopsy findings included kernicterus, bile stasis, and intussusception, which was the cause of death. The second weighed 2 lb. 6 oz. and received a course of cortisone therapy for physiological jaundice from the second to the eighth days. Signs of peritonitis appeared on the 10th day, and he died on the 16th day with acute ulcerating enterocolitis with acute perforation of the sigmoid colon. The third weighed 2 lb. 4 oz., and treatment was started on the fourth day. The infant died on the sixth day with no significant pathological findings other than prematurity.

COMMENT

Elevation of serum bilirubin has grave significance in its correlation with the incidence of kernicterus.[4] Since this disease has been recognized not only in erythroblastosis fetalis, but also in cases without hemolytic disease,* the ability of cortisone to lower the serum bilirubin was considered an important indication for its trial in this age period in all cases of jaundice. It has been reported to act as a cholegogue in cases of hepatocellular disease in older children and adults,† and it may also lower the serum bilirubin by means other than increasing the excretion of the pigment.[10] These effects, however, are not evident in the cases herein reported, and the results suggest that this age group is incapable of such a response. Replacement transfusion remains the only effective means of diminishing the serum bilirubin during this critical period.

Large doses of hydrocortisone failed to prevent the neonatal decline in hemoglobin and the hypoplasia of erythroid elements in the marrow of these infants. These observations are consistent with the experiments of Contopoulos and his co-workers in newborn rats in which adrenal cortical extract was found to be ineffective in the prevention of neonatal anemia.[11]

While blood corticoid values are low in the newborn infant when compared with older infants and adults, there is no evidence that this situation is harmful to the patient.[12] The present experiments demonstrate further that these patients are actually resistant to certain of the actions of hydrocortisone in pharmacological doses.

There have been serious complications reported following the use of cortisone for three weeks or more after birth in the form of lack of growth and susceptibility to infection.[13] With the regimen of five to seven days used here this was not observed, but it is possible that the perforation of the small bowel in one of the infants was related to the administration of the drug. Thus certain dangers are attached to the administration of hydrocortisone in these babies, and in the series of patients with jaundice reported here results do not seem to warrant its use.

SUMMARY

The effects of hydrocortisone are evaluated in erythroblastosis fetalis and physiological jaundice of the newborn. In neither group was there any definite effect on the bilirubin level or on the red cell production.

Pfizer Laboratories, Division of Chas. Pfizer & Company, Inc., provided the hydrocortisone for this study.

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A Genetic Study of Celiac Disease

Incidence of Celiac Disease, Gastrointestinal Disorders, and Diabetes in Pedigrees of Children with Celiac Disease

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and
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Celiac disease in more than one member of a sibship has been frequently reported in the medical literature. Thompson in 1951 published a list of the reported cases. There were several instances among twins, siblings, cousins, and even among parents of the propositi.[1] Recently it has been observed that, apart from the typical form of celiac disease, there is, among the immediate family and more distant relatives of patients with this condition, a tendency toward a variety of gastrointestinal disturbances. The present investigation represents an attempt to study the type and frequency of such gastrointestinal disturbances.

The incidence of diabetes mellitus in pedigrees of children with celiac disease is believed to be higher than the expected incidence in the general population.* Data on this question were also obtained.

The pedigrees of 50 children with celiac disease and of 50 controls were studied and compared. Because of the known difficulty of establishing with precision a diagnosis of celiac disease, the selection of cases was made with care. The patients included in the study were chosen from among cases of celiac disease diagnosed at Babies Hospital between the ages of 6 months and 5 years. From this group they were selected according to the availability of the families for interviews. They were all white except one girl, who was partly Negro. All these cases fulfilled our clinical and laboratory criteria for the diagnosis of celiac disease.[3] Many of them belonged to the early group of patients studied in detail by Andersen and her associates.†

Fifty cases were included in this series. Half of them were typical examples of the severe form of celiac disease; the other half belonged to the group of mild celiac disease or starch intolerance.

The presence of steatorrhea was the criterion used for differentiating between the two groups. The classic severe form of celiac disease is characterized by the presence of steatorrhea. The mild form of celiac disease shows little or no steatorrhea. In both there is an abnormal amount of starch in the stool. The fecal fat and starch determinations were done by microscopic examination of the stools, with use of the method described by one of us.[5]

The family pedigrees were obtained in personal interviews with the parents of the affected children. Letters were sent to the parents with whom interviews were desired, explaining the purpose of the study and requesting their cooperation. In the course of the years an excellent rapport with many of these families had been developed, and there was no difficulty in collecting the information requested. Many of the parents were particularly anxious to help, and they made inquiries among their relatives in an effort to provide accurate data.

All of the interviews were conducted by one of us. The father and mother were interviewed separately, since there was less reluctance in discussing family illnesses or personal symptoms when the other parent

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* References 1 and 2.

† References 3 and 4.

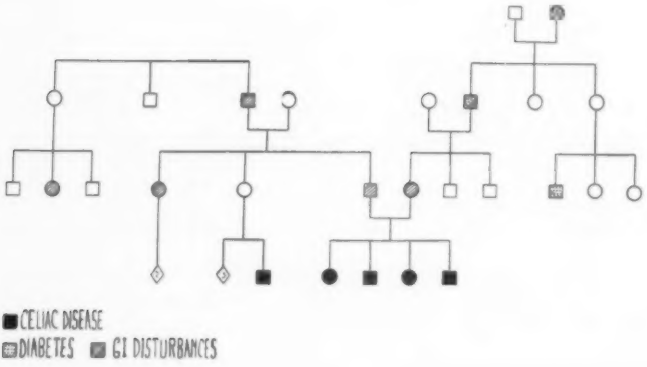

Fig. 1.—Pedigree of patient with celiac disease.

was not present. Thus, in some cases we were able to obtain information that the other parent had withheld, being afraid that he or his relatives would be considered responsible for the celiac trait.

The controls were carefully selected. The clinic population was considered to be unsatisfactory, because of the difficulty in achieving in a brief interview the degree of cooperation necessary to obtain a complete pedigree. Moreover, in most cases only one parent was available, and so the data on the family of the parent not present would have been incomplete or unreliable. It was also unlikely that other interviews or further contacts could have been arranged.

As controls the offspring or the siblings of members of the hospital resident and nursing staff were used. It was expected that information obtained in this way could be considered fairly accurate. The age range for the control propositi was from 1 to 15 years. They all belonged to the Caucasian race. The pedigrees so obtained were complete and therefore were believed to be more nearly comparable to those of the test group than any other controls available. The individual propositi with a clinical history or symptoms suggestive of celiac disease or diabetes, or other chronic illness that could have produced gastrointestinal symptoms, were excluded. The controls were otherwise unselected.

In studying the pedigrees of children with celiac disease, it was found, very consistently, that there was a family tendency toward certain gastrointestinal disturbances (Figs. 1 to 6). A history of recurrent unexplained episodes of diarrhea, or loose stools, sometimes precipitated by emotional factors ("nervous stomach"), was frequently present, particularly in the parents of the propositi. Many complained of urgency in relieving the bowels immediately after meals. Diarrhea specifically related to the intake of cow's milk was reported in a few cases. Difficult digestion after eating fried foods, or intolerance to fats, was sometimes ob-

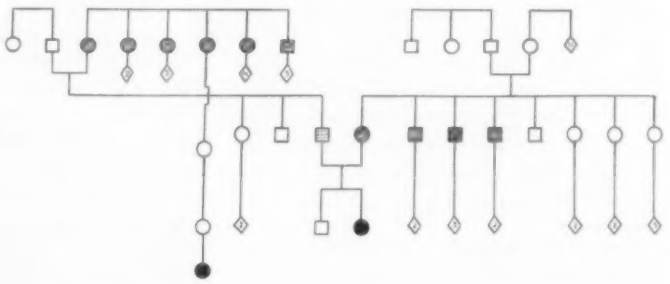

Fig. 2.—Pedigree of patient with celiac disease.

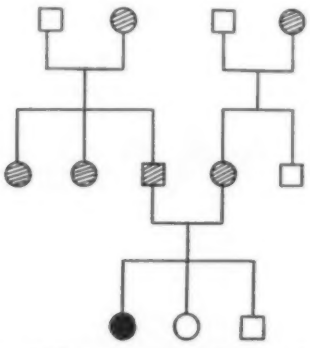

Fig. 3.—Pedigree of patient with celiac disease.

served. This had been occasionally interpreted as the result of gall-bladder dysfunction. Allergy or intolerance to a variety of foods was also reported. There were several instances in which the clinical history and the symptoms described were compatible with celiac disease. In some cases the picture was so typical that the person acting as informant volunteered this impression.

The real frequency of diarrhea or "poor digestion" was probably higher than observed. Obviously, it would be difficult to obtain accurate information unless all the members of a given pedigree were personally interviewed. Modesty may restrain some persons from discussing with their relatives symptoms of this nature. Lack of close contact between the person acting as informant and other members of the family may easily be the source of inadequate or distorted information. The validity of information thus obtained is hard to evaluate. It is also difficult to interpret symptoms, sometimes only vaguely described. Clinical confirmation of the gastrointestinal disturbances discussed is lacking. Nevertheless, the frequency and consistent similarity of such complaints in the celiac pedigrees is impressive.

The typical gastrointestinal symptoms present in many of the pedigrees of celiac patients were grouped in four categories. This was done in an effort to simplify their evaluation and to facilitate comparison with the control group. These categories are as follows:

(1) Unexplained recurrent episodes of diarrhea
(2) Clinical history and symptomatology compatible with celiac disease
(3) Intolerance to certain foods (this group includes cases of diarrhea secondary to the ingestion of milk, as well as those with complaint of recurrent difficult digestion following the intake of some specific food)
(4) Intolerance to fats and fried foods

In the control group there were four cases with vague gastrointestinal symptoms, and they were included in a separate category.

The incidence of the gastrointestinal symptoms falling in these four categories, among the siblings, parents, siblings of parents, and grandparents of the propositi, in both the celiac and the control pedigrees was analyzed (Tables 1 and 2). The final results were compared, and it was observed that the incidence of these specific gastrointestinal symptoms in the celiac pedigrees was much higher than those in the control pedigrees.

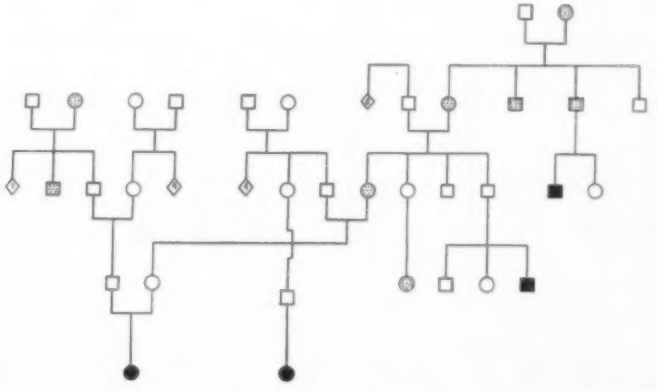

Fig. 4.—Pedigree of patient with celiac disease.

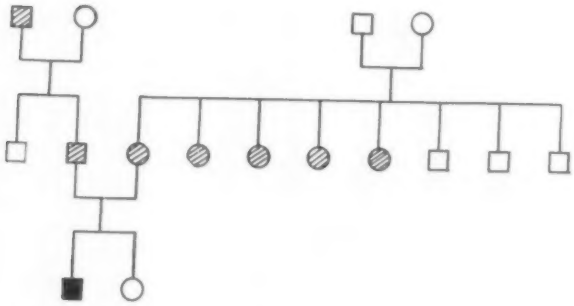

Fig. 5.—Pedigree of patient with celiac disease.

the difference in each comparison being of statistical significance (Table 3).

The 50 celiac propositi had among them a total of 59 siblings, of whom 14 had had celiac disease diagnosed. Five of these had severe celiac disease, and the rest had starch intolerance. This represents an incidence of 23.7%. There were five instances among the parents of the celiac propositi (5%) and five others among the siblings of these parents (1.1%), in which the evidence for celiac disease was strong on the basis of the past history and the symptomatology. No cases of celiac disease were found in the control pedigrees.

In Thompson's survey a history of celiac disease in early childhood was present in 13% of the sibs of celiacs, in 6% of their parents, and in 1% of their grandparents.[3]

The incidence of peptic ulcers, gall-bladder disease, and allergies in general was also investigated in both the control and the celiac sibships. No significant difference was observed between the two groups.

In 27 of the 50 celiac sibships studied there was a diabetic family history (Figs. 1, 2, 4, and 6). In 14 of these pedigrees two or more persons were found to have this condition. Fifteen pedigrees with diabetes were present among the control group. Seven of these sibships showed diabetes in two or more members. The difference in the incidence of diabetes among the celiac and the control pedigrees, taken as a whole, is of statistical significance ($P<0.02$).

These figures are suggestive of an association between celiac disease and diabetes, but, if analyzed, they are not fully convincing.

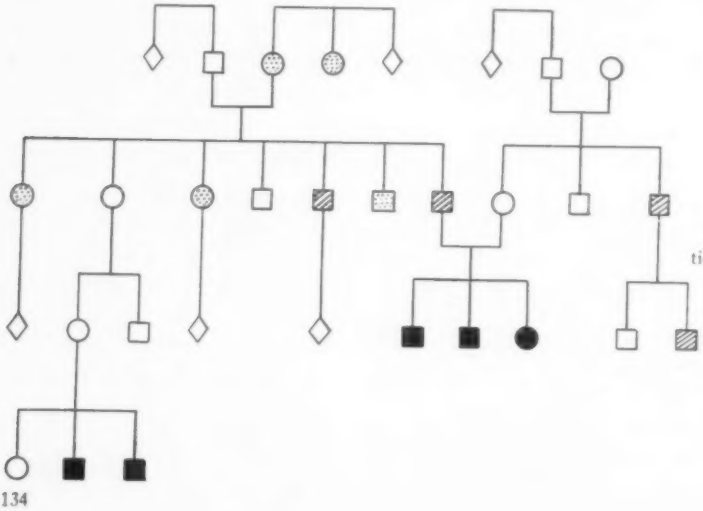

Fig. 6.—Pedigree of patient with celiac disease.

TABLE 1.—*Incidence of Gastrointestinal Disturbances in Celiac and in Control Pedigrees*

Celiac pedigrees	Total No.	Unexplained Recurrent Diarrhea	Probable Celiac Disease	Intolerance to Certain Foods	Intolerance to Fats	Nonspecific GI Disturbances	GI Disturbances in General	
							Cases, No.	Per Cent
Parents	100	29	5	4	5	..	43	43.0
Sibs of parents	440	25	5	2	6	.	48	10.0
Grandparents	200	14	..	2	5	.	22	11.0
Control pedigrees								
Parents	100	6	..	3	0	..	9	9.0
Sibs of parents	328	5	..	1	1	4	11	3.3
Grandparents	200	3	..	0	0	..	3	1.5

TABLE 2.—*Incidence of Celiac Disease Among Siblings of Celiac and Control Propositi*

Propositi	Siblings of Propositi, No.	
	With Celiac Disease	Without Celiac Disease
Propositi with severe celiac disease (25 cases)	5	27
Propositi with starch intolerance (25 cases)	9	18
Total no. of propositi with celiac disease (50 cases)	14	45
Control propositi (50 cases)	0	69

The incidence of diabetes varies according to the age group, and the age factor was not considered in the above evaluation. The size of the pedigrees compared is another point that deserves consideration.

To avoid these sources of error we limited the survey to the propositi and their siblings, parents, siblings of parents, and grandparents (Table 4). Since the celiac and control propositi were aged 1-15 years, it is logical to assume that the parents and the grandparents in both series are in comparable age groups. There were no diabetics among the celiac propositi. Among their siblings there was only one case of diabetes; there was none in the control group. Two suspected diabetics were present among the parents of the celiac propositi; there was none among the parents of the control group. In the celiac pedigrees the incidence of diabetes among siblings of the parents was 1.1%, compared with 0.6% in the controls. Among the grandparents the incidence was slightly higher in the celiac group (7.5% compared with 6.0%). Thompson, in Canada, made a survey (1951) on the incidence of diabetes in celiac pedigrees and obtained figures similar to ours (Table 5). She compared her results with the figures reported by the National Health Survey of 1935-1936 and noted that the incidence of diabetes among members of the celiac pedigrees was higher than the expected incidence for similar age groups. It is believed that the frequency of diabetes today is higher than the results reported in the 1935-1936 survey, but there are no comprehensive current data. There are available figures of case-finding programs using both urine and blood sugar tests, but their results are not comparable to Thompson's or ours, because we only considered known diabetics. These community studies were made in Oxford, Mass., and in certain areas of Canada.‡

‡ References 6-11.

TABLE 3.—*Incidence of Gastrointestinal Disturbances in Control and Celiac Pedigrees*

Relationship to Propositi	Control Pedigrees		Celiac Pedigrees		P
	Without GI Disturbances	With GI Disturbances	Without GI Disturbances	With GI Disturbances	
Parents	91	9	57	43	<0.001
Sibs of parents	317	11	392	48	<0.001
Grandparents	197	3	178	22	<0.001

TABLE 4.—*Incidence of Diabetes in Celiac and Control Pedigrees*

Group Analyzed	Parents			Sibs of Parents			Grandparents		
	Without Diabetes	With Diabetes	% With Diabetes	Without Diabetes	With Diabetes	% With Diabetes	Without Diabetes	With Diabetes	% With Diabetes
Severe celiac disease	50	0	...	186	4	2.1	93	7	7.0
Starch intolerance	48	2	4.0	249	1	0.4	92	8	8.0
Total no. of cases with celiac disease	98	2*	2.0	435	5	1.1	185	15	7.5
Controls	100	0	...	324	2	0.6	188	12	6.0

* Diabetes only vaguely suspected.

TABLE 5.—*Incidence of Diabetes in Thompson's and in Babies Hospital Series*

Group	Total No.		Diabetics		Per Cent with Diabetes	
	T.*	BH *	T.	BH	T.	BH
Celiacs	119	64	2	0	1.7	0
Sibs of celiacs	102	45	2	1	1.9	2.2
Parents	189	100	1 (+1)†	2‡	0.5	2.0
Grandparents	361	200	20	15	5.5	7.5

* T., Thompson's [3] series; BH, present series.
† "Potential diabetic."
‡ Diabetes only vaguely suspected.

Among our control group the frequency of diabetes was higher than the reported incidence in the National Health Survey of 1935-1936. This difference may be due to the small sample. In an effort to reach a more definite conclusion by studying a larger sample, control children were chosen at random among the Caucasian population attending the general pediatric clinic. Their ages ranged from a few days to 14 years. Patients with diabetes, celiac disease, or cystic fibrosis of the pancreas were excluded from the survey. Otherwise the controls were unselected. The examining physician recorded on special cards any history of diabetes among the siblings, parents, or grandparents, as well as their ages. No attempt was made to confirm the diagnosis.

A total of 207 control families were studied. In 19% of these pedigrees there was a history of diabetes in at least one of the members. Among siblings of the propositi there were no diabetics. The incidence of diabetes in the parents and grandparents was 0.4% and 4.9%, respectively. These figures are similar to the ones obtained in the previous group of controls (Tables 4 and 6).

Among the total number of controls represented by 257 pedigrees, there were 50 with diabetes in the parents, grandparents, or siblings of the propositi. Fifteen celiac pedigrees out of fifty showed diabetes among comparable members. The χ-square value for the above figures is not statistically significant: P=0.10 (Table 7). The difference in the incidence of diabetes among the parents of the celiacs and of the controls was difficult to evaluate because in the two cases of diabetes in the celiac group the diagnosis was only vaguely suspected. The incidence of diabetes for the grandparents of celiacs was higher than for the controls, but the difference was not of statistical significance. There was only one diabetic among the siblings of celiacs, and there was none in the control group.

The analysis of the figures provided by this survey proves that there is a high inci-

TABLE 6.—*Incidence of Diabetes Among Celiac and Control Pedigrees*

Group Analyzed	Parents		Grandparents		Siblings	
	Without Diabetes	With Diabetes	Without Diabetes	With Diabetes	Without Diabetes	With Diabetes
Celiacs (50 pedigrees)	98	2*	185	15	45	1
Controls (257 pedigrees)	506	2	956	52	337	0

* Diabetes only vaguely suspected.

TABLE 7.—*Incidence of Diabetes Among Celiac and Control Pedigrees*

Group Analyzed	Pedigrees with Diabetes in Parents, Grandparents, or Sibs of Propositi		
	No. of Pedigrees	Per Cent	*P*
Celiacs (50 pedigrees)...	15	30	0.10
Controls (257 pedigrees)	50	19	

dence of celiac disease and of certain gastrointestinal disturbances in pedigrees of patients with the celiac condition.

The possibility of an association between the incidence of celiac disease and the incidence of diabetes in members of the same pedigree was not confirmed. Such a relationship seems unlikely, but no definite conclusions could be reached from the evaluation of the figures obtained in this study.

SUMMARY

The pedigrees of 50 children with celiac disease and of 50 controls were studied with respect to the frequency of gastrointestinal disturbance and of diabetes. A significantly high incidence of celiac disease, recurrent unexplained diarrhea, and intolerance to fats and certain other foods was found in the pedigrees of children with celiac disease. The incidence of diabetes is not significantly greater in the celiac than in the control pedigrees.

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Constitutional Precocious Puberty in the Male

Report of Three Cases

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Constitutional (familial) precocious puberty in the male is a rare entity; a review of the literature reveals only nine reports on this condition. Stone,[1] in 1852, reported the first case, a 4-year-old boy whose father had also been affected. It was not mentioned again until 1922, when Reuben and Manning [2] reported a similar case. Orel,[3] in 1928, reported its occurrence in two additional families. Rush and his co-workers, in 1937,[4] reported on a family in which premature development had been noted in four generations. Sigrist,[5] in 1940, reported on an additional family. Engstrom and Munson, in 1951,[6] described still another family, with the father and two sons affected. In 1952, Jacobsen and Macklin reported a single family in which 27 members over a span of five generations had been affected,[7] and in the same year, Walker [8] reported a family with father, son, and five other members in three generations involved. Mortimer,[9] in 1954, reported on an additional family in which six members were affected in four generations.

CASE 1.—This boy was 18 months old on his initial visit. At the age of 13 months, the parents noticed that the child's penis was enlarging and his voice was getting husky. At the age of 18 months, they noted that he was larger than the other siblings in the family had been and that he had developed a small amount of fine, downy pubic hair (Fig. 1).

The family incidence of this condition is shown in Chart 1. It is unique because although only the males were affected, the genetic trait was transmitted through only the female members of the family. In all cases previously reported, the genetic trait was transmitted either by the males of the families or through both sexes.

Physical examination showed a well-developed, well-nourished boy who appeared older than his stated age of 18 months. Blood pressure, temperature, pulse, and respirations were all within normal limits. His height was 33 in., and his weight was 29½ lb. There was no facial or axillary hair. The skin was free of acne. The genitalia consisted of a 6 cm. penis, enlarged testes, and a small amount of fine pubic hair. Androgenic activity was evidenced by advanced muscular development and a deep, husky voice, as well as his sexual maturation.

The physical and laboratory data for the initial visit and two six-month follow-up visits are recorded in Table 1. All the urinary determinations were within normal range for the age of the patient. The remarkable gain of 6½ in. in height and 13 lb. of weight in the year he was under observation was at the expense of a six-year advance in bone age. This is a striking illustration of the finding that precocious puberty is accompanied by rapid

TABLE 1.—*Laboratory and Physical Data on Case 1*

	Age 18 Mo.	Age 24 Mo.	Age 30 Mo.
Urinary 17-ketosteroids, mg./24 hr.	2.6	1.6	1.6
Urinary 17-hydroxycorticoids, mg./24 hr.	0.3	0.3	0.3
Urinary gonadotropin titer, M.u./24 hr.	<13	<4	Not done
Circulating eosinophile count/cu. mm.	87 (nonfasting)	255 (fasting)	Not done
Height, in.	33	36	39½
Weight, lb.	29½	35	42
Bone age, yr.	2	Not done	8
Sella turcica	Normal	Not done	Not done

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This study was aided by a grant from Ciba Pharmaceutical Products, Inc., and was executed under the supervision of Dr. Robert B. Greenblatt, Department of Endocrinology, Medical College of Georgia.

Fig. 1.—Case 1 when first seen, at age 1½ years.

growth with early bone maturation and epiphysial closure, giving a final result of diminished stature, even though during the growing phase the stature of the child is far greater than that of other children of the same age.

Case 2.—This boy was first seen at 4½ years of age. He was normal at birth, and his development was normal until the age of 22 months, when the parents noticed that he was growing rapidly. By the age of 30 months, the child's penis was enlarging and his voice was becoming harsh. Pubic hair was noted just prior to the age of 3 years.

Chart 2 illustrates the familial incidence in this case. As in Case 1, the family history revealed that only males were affected, and the genetic trait was transmitted from generation to generation through the females.

Physical examination showed a well-developed, well-nourished boy who appeared much older than his stated age of 4½ years (Fig. 2). Blood pressure, pulse, respirations, and temperature were all normal. His height was 53 in. and his weight was 65 lb. There was a fine, lanugo-like hair growth on the upper lip, but none was present elsewhere on the face or in the axillae. The skin was free of acne. The genitalia were of adult proportions: the penis was 7 cm. long, pubic hair was present, and the testes were well developed.

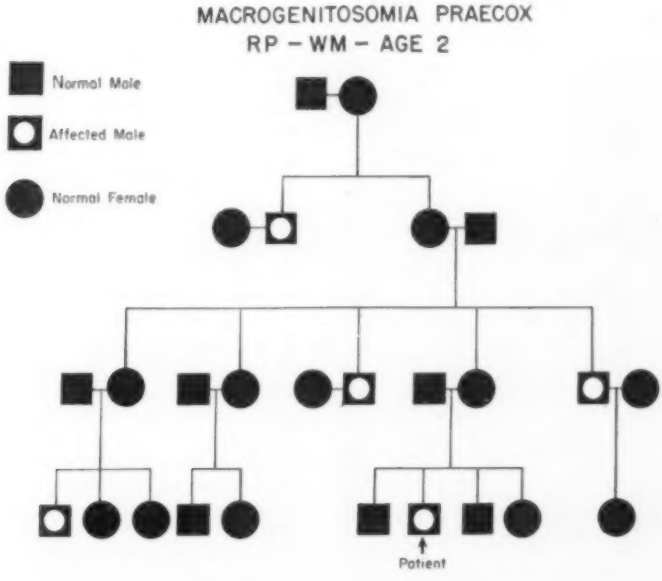

Chart 1.—Familial incidence of precocious puberty in Case 1.

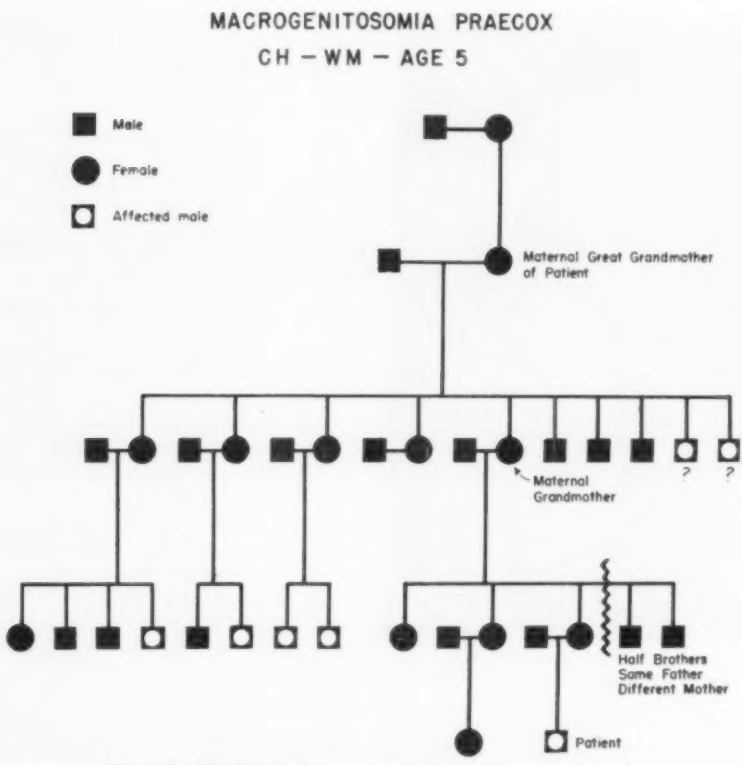

Chart 2.—Familial incidence of precocious puberty in Case 2.

Fig. 2.—Case 2 when first seen, at age 4½ years.

The essential physical and laboratory examinations for a 10-month follow-up of this case are shown in Table 2. This child was seen at a more advanced stage of the illness, but again all urinary hormone assays were within the limits of normal for his age except for the 17-ketosteroids, which agreed with his puberal changes.

A testicular biopsy was done on the right testicle on his initial visit and revealed considerable maturation of the spermatogenic series to the spermatid stage, with no mature sperm identified. The tubules were enlarged, approximating adult proportions. The Leydig cells appeared normal.

CASE 3.—On his initial visit, this boy was 4½ years old. His parents first noted the appearance of pubic hair when he was 12 months old and deepening of his voice at the age of 24 months.

The incidence of precocity in this family is noted in Chart 3. In this instance, the genetic transfer was accomplished through both male and female carriers, but the disease again only affected the males.

On physical examination, he was a well-developed, well-nourished boy with adult genitalia, appearing much older than his chronological age (Fig. 3)

TABLE 2.—*Laboratory and Physical Data on Case 2*

	Age 4½ Yr	Age 5 Yr.	Age 5¼ Yr.	Age 5½ Yr.
Height, in.	53½	54½	55¾	..
Weight, lb.	66	71	71	..
Urinary 17-ketosteroids, mg./24 hr.	3.5	4.6	3.5	4.2
Urinary 17-hydroxycorticoids, mg./24 hr.	0.8	0.8	1.4	2.0
Urinary gonadotropins, M.U./24 hr.	..	<4	..	..
Serum cholesterol, mg./100 cc.	258	..	..	..
Eosinophil count/cu. mm.	..	150	175	..
Bone age, yr.	12½	..	..	Over 13
Sella turcica	Normal	..	..	..

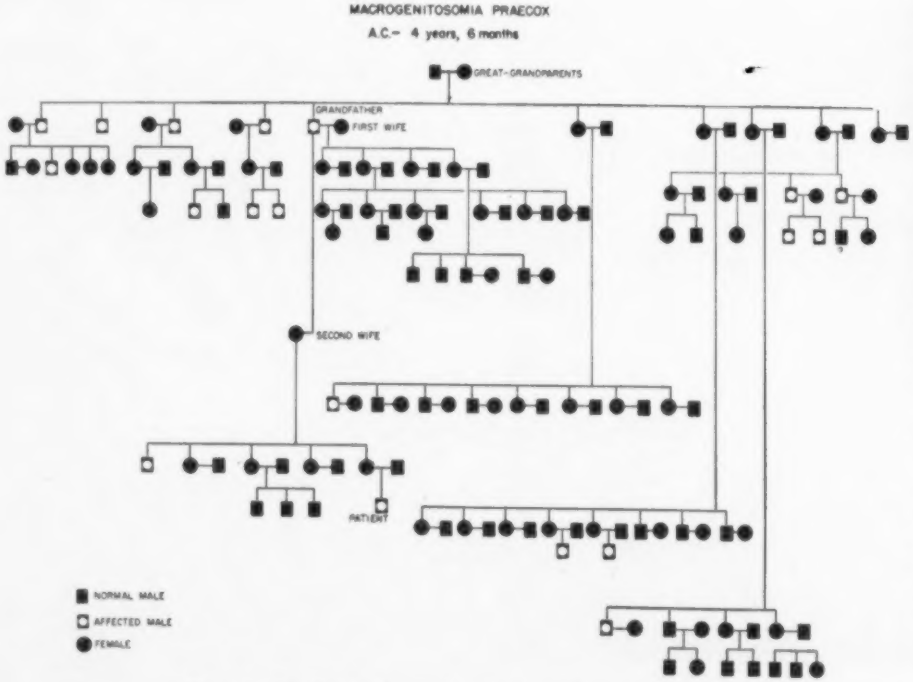

Chart 3.—Familial incidence of precocious puberty in Case 3.

Fig. 3.—Case 3 when first seen, at age 4½ years.

TABLE 3.—*Laboratory and Physical Data on Case 3*

	Age 4½ Yr.
Urinary 17-ketosteroids, mg./24 hr.	5.7
Urinary 17-hydroxycorticoids, mg./24 hr.	1.0
Urinary gonadotropin titer, M.U./24 hr.	<6.4
Circulating eosinophil count/cu. mm.	175 (fasting)
Height, in	56
Weight, lb.	67
Bone age, yr.	13
Sella turcica	Normal

His blood pressure, temperature, pulse, and respirations were all normal. He was 55 in. tall and weighed 67 lb. He had minimal hair on the face, slightly increased on the upper lip, a little axillary hair, a large amount of pubic hair in a female pattern, and a moderate growth of extremity hair. His voice was quite deep. There was no acne. His genitalia approached adult size, consisting of a 9 cm. penis and well-developed testes measuring 3×2 cm. The pertinent physical and laboratory data are listed in Table 3. A testicular biopsy was obtained and showed considerable spermatogenesis with many spermatids and an occasional mature sperm. The Leydig cells appeared normal (Fig. 4).

This case was also first seen in a rather advanced stage, yet all the hormone assays were within normal limits for his age except the 17-ketosteroids, which were consistent with his development.

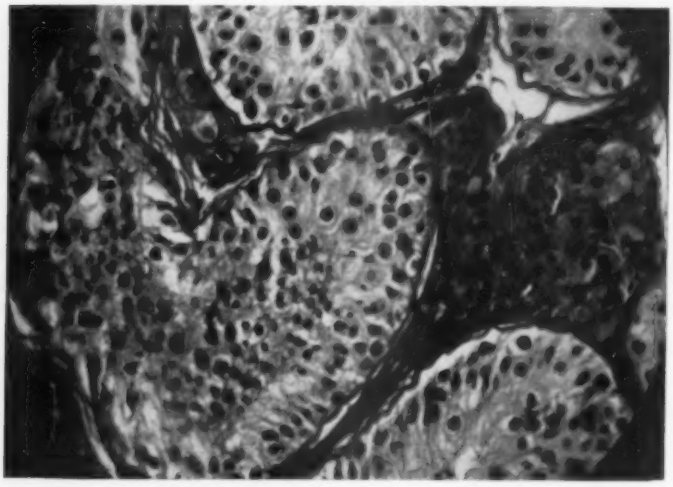

Fig. 4.—Testicular biopsy of Case 3. Note normal-appearing Leydig cells, and a few mature sperm scattered throughout the seminiferous tubules.

COMMENT

Precocious puberty in the male has been classified by Wilkins [10] into two main groups: (*a*) true or complete precocity, resulting from early activation of the pituitary to release its gonadotropic hormones, and (*b*) incomplete precocity, or virilism, due to abnormal secretion of androgenic substances by testicular or adrenal tumor.

True precocious puberty has been further divided into two groups: (*a*) familial, in which there is a demonstrable genetic basis for the precocity, and (*b*) idiopathic, where no such familial incidence can be elicited.

The three cases herein reported have been shown to have a familial incidence and were caused by a premature gonadotropic hormone stimulation, as evidenced by the normal hormonal values for the age of the patients and the enlarged mature gonads. Thus, they fall into the classification of true familial precocious puberty. The first two differ from the previously reported cases in that whereas the male only was affected, the genetic transfer from generation to generation was accomplished by only female carriers.

In general, true precocious puberty in the male is accompanied by normal or high androgen levels for that age group, whereas the incomplete or virilism type is accompanied by higher than normal levels of androgenic hormones. It is readily apparent that differentiation of these two main types of precocity is important, since removal of the abnormal tissue is indicated in the virilism type, whereas true precocity is characterized by normal tissue functioning prematurely, and removal of the normal tissue is not indicated.

SUMMARY

Three cases of familial precocious puberty are presented, occurring in boys 1½, 4½, and 4½ years of age. The first two cases

differ from those previously reported in that the genetic tendency in each instance was transmitted only by the female members of the family. In the third case, the genetic transfer was accomplished by both males and females. In one instance, mature sperms were found in the testicular biopsy.

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Emotional Factors in the Etiology and Treatment of Lead Poisoning

A Study of Pica in Children

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In order to treat lead poisoning in children adequately, it is necessary to consider the factors which cause children to ingest lead-containing substances. Frequently children hospitalized for lead poisoning are treated for their medical illness, only to return with the same history, and it is found that they have continued to ingest substances containing lead.

Six cases of lead poisoning admitted to Children's Hospital have been studied from the psychiatric aspects. In all of the cases, a history of pica (an abnormal appetite for substances not fit for food) was present. Children go through a period in their development, beginning at about age 6 months, when it is normal for them to put objects in their mouths. This period ends at about the age of 12 months. Gesell[1] states, "Oral patterns become more or less restricted to the feeding situation at about the end of the first year; toys and hands, except when thumb-sucking is a persistent pattern, go less frequently to the mouth." Until about the end of the first year of life, lead poisoning must be regarded as accidental. It is one of the many accident hazards which parents need to be informed of by their physicians in terms of the sources of lead and its dangers. The ages of the children in this study at the time of diagnosis of lead poisoning ranged from 18 to 38 months. The purpose of this study was to learn something of the factors which lead to the persistence of oral activities beyond the normal developmental period.

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METHODS

The basic study which was attempted in each case included one or two interviews with the mother, psychological studies of the child and of the mother, and a psychiatric playroom interview with the child. Of the six cases herein reported, the complete study was carried out in three cases; the other three were less complete, but gave significant information. The parents and child were seen for psychotherapy after the study in one case. In another, the mother of a very young child was seen in therapy. Types of contact included in the study for each case are listed in the Table.

Types of Contact Included in the Study of Each Case

Cases	1	2	3	4	5	6
Interviews with mother	+	+	+	+	+	+
Psychological tests, child	+	+	+	..	..	+
Psychological tests, mother	+	+	+	..	..	..
Psychiatric playroom interview	+	+	+	+	..	+
Psychotherapy with mother	+	..	..	..	..	+
Psychotherapy with child	..	..	..	..	..	+

The interviews with the mother were for the purpose of getting detailed history of the sort obtained routinely for a diagnostic psychiatric study of the child. This includes information about the problem the child presents (in these cases, pica), its handling, the developmental history (from the physical, mental, and emotional aspects), habit and training patterns, the background and patterns of emotional relationships in the family. Although two of the mothers were seen for psychotherapy over a period of time, in all the diagnostic interviews attempts to help the mother to gain insight into the problems were also made.

Psychological studies of the four children examined were based on a psychometric approach to the evaluation of developmental status, with a qualitative analysis of the child's performance in different types of subtests and recording of general behavioral observations in the test situation. The tests were selected on the basis of their appropriateness in terms of the age and interests of the child and in terms of their adequacy for sampling both verbal and nonverbal abilities. One or more of the following tests was administered to each child, as seemed appropriate: Minnesota Pre-School Scale, Gesell Developmental Schedules, Cattell Infant Intelligence Scale, Vineland Social Maturity Scale, Merrill-Palmer Scale of Mental Tests, and Stanford-Binet, Form L.

The three mothers given psychological examinations were evaluated from the standpoint of personality and emotional characteristics on the basis of the Rorschach examination. Although the time available for the studies did not permit the administration of individual intelligence tests, such as the Stanford-Binet or the Wechsler Bellevue Scales, an estimate of each mother's intellectual functioning level was made on the basis of educational history and Rorschach findings, supplemented by the Otis Self-Administering Intelligence Test, given to two mothers, and the Kent E-G-Y, given to one.

REPORT OF CASES

CASE 1.—This boy was hospitalized for a minor surgical procedure, and lead poisoning was found incidentally. He was seen for study two months later, at the age of 20 months. The source of the lead was paint which he chewed off his crib. There were two outstanding things found in the examination of the child: (1) his response to many toys of putting them in his mouth and (2) his complete and happy acceptance of leaving his mother at an age when the usual response to such separation is anxiety and protest. He was retarded in all aspects of development except motor development. There was noticeable drooling. The mother was of average intelligence, but she had patterns of passive dependent relationships with a series of men in order to have her needs met. She was also very dependent on her own mother. She seemed to feel that her needs would be met if she were passive and compliant. Instead of relating to the child in a close personal relationship, the mother responded to his indications of anxiety on any basis by putting the bottle in his mouth. This happened very frequently, both day and night, whenever he indicated by being fussy that he had some needs. Because of the drooling and the retardation of development to about the 14-month level, it seemed likely that there was organic damage, possibly due to the chronic lead poisoning.

Following the original study, the mother was seen at intervals of one to two weeks for guidance in handling the child. Emphasis was on gradual weaning from the bottle and on trying to relate to the child herself rather than giving him a bottle whenever he became fussy. Reevaluation at the age of 23 months showed that he had abandoned his indiscriminate hand-to-mouth activities and participated with the examiners in play with toys in a much more organized way. His mental age had increased by 5 months (up to 19 months).

CASE 2.—This patient was first hospitalized at the age of 25 months, for lead encephalitis. She was studied at the age of 30 months, at which time she was again hospitalized, this time for a convulsive seizure. On second admission, the child showed an exaggerated reaction to hospitalization, screaming continually on the ward and creating a nursing problem. By the time of the study, she was in the phase of withdrawal and was not very related to anyone. Her hospital reaction indicated that she was reacting severely to the loss of her dependency relationship to her mother and in a more violent and disorganized way than most children.

The child had been delivered by a difficult breech delivery. It could not be determined whether the finding of mild organic brain damage was on the basis of birth trauma or on the basis of damage due to the lead. She was still using her mouth for sensory perception to feel the shape and texture of objects like those children who have disturbances in their other sensory perceptions. This was in addition to clinging to her mouth activities in a pleasurable way as was shown in her wanting to suck the doll bottle. Her pica had begun at nine months when she was crawling. She began to put crayons, pencils, plaster, and dirt in her mouth and to suck other objects. It was evident that the mother did not supervise the child closely enough to prevent the pica.

The history revealed pertinent information as a possible explanation for the persistence of the pica beyond the first year. In effect, this youngster was an only child until the age of 14 months, at which time three older siblings who had been out of the parents' home until then returned to live in it. Then, when the child was 16 months old, a new baby was born. It may be assumed that she very suddenly had a great deal of competition from her siblings in terms of getting her needs met. There also seemed to be a lack of differentiation by the mother between the new baby and the patient, as was evidenced by her weaning them both from the bottle at the same time, as the most convenient way to handle it. Weaning occurred when the patient was just less than 2½ years old. Until that time she had walked around the house sucking the bottle much of the time.

The mother was of borderline intelligence, and she was passive, dependent, and outwardly conforming. She handled her hostility in terms of avoidance, such as failing to follow up on medical or psychiatry appointments. Her marriage had been at the age of 14, and she seemed to relate to people on a biological level. She did not recognize either the child's needs in terms of health or her needs in terms of personal relationships. She said that she was glad that her husband was affectionate with the two small children, but she herself did not hold them much, since she did not want them to be spoiled. The child seemed to have turned to oral activities in lieu of a more satisfying relationship to meet her dependent needs.

Case 3.—This patient was hospitalized at the age of 26 months for poliomyelitis, and subsequently she was found to have lead poisoning. A history of pica was elicited which dated back to the age of 1½ years, at least. At that time the family home burned, and they lived for a few months in a house where the child ate plaster off the walls. Also at this time, the mother worked for about a month, and the child was boarded in the home of relatives, except for week-ends. This was the first separation from the mother. Two to three months prior to the child's hospitalization, her mother began working again, and the child stayed for a part of each day with her aunt. In addition to the eating of plaster, she also chewed on her toys and ate dirt whenever she was put in the yard to play. If her mother was near her, she would stop eating dirt. The mother had enjoyed eating dirt herself until the age of 8 or 9 years, so she condoned this activity on the part of the child out of her own early experience. The son of the aunt in whose home the child was staying for day-care just prior to hospitalization also ate plaster until he was a large boy. At times the child was quite unhappy about the separations from her mother. She may have returned to a pattern of oral satisfactions as a result of anxiety about the second separation from the mother.

She was a premature baby and a very active child prior to this illness. It was not possible to exclude organic brain damage prior to the lead poisoning. This child approached the average in verbal abilities, but was significantly retarded in motor ability and form perception. Her social relations were immature, being those of a 15-month-old child rather than 30 months, her age when tested. The mother stated that the whole family babied her and did not frustrate her in any way. The mother's intellectual functioning was at a dull-normal level.

Cases 4 and 5.—These two siblings were both admitted for lead poisoning. The first one entered at age 3 years; the second, five months after the first, at age 26 months. The mother was quite insecure and had relied on reading books on how not to spoil her children and on rigid methods in her handling of them. She demanded performance of them in terms of giving up at an early age the usual body satisfactions, including sucking. Neither child was held for the bottle, and both were weaned at 11 months. The second child was toilet-trained before she walked, by 14 months. The mother described both children as very stubborn. They were punished by switching and by being put in the closet for all misdemeanors. There was a lack of individualization of handling the three siblings in the family. The mother put them all on the same schedule, including two naps a day, though they cried themselves to sleep. The mother let us know about what she considered the laxity of the hospital personnel in letting the children lose their training in toileting, table manners, and handling of genitals. The mother seemed very rigid and controlling in her relations with the children, and she seemed to interpret as bad any deviations in the children's behavior which she did not understand. The second child was described as being related chiefly to some favorite toy animals, and she did not want to be touched by anyone. The mother seemed unaware of her own hostility and of her lack of any warm responsive relationship to her children, as well as of her isolation from other people. The children turned chiefly to mouth activities of their own, such as nail-biting, tongue-sucking, and chewing on various objects, including matches, paper, the bed, and peeling paint.

Case 6.—This boy was first hospitalized for lead poisoning at the age of 3 years. He was referred to the psychiatry department a year later following two additional hospitalizations related to the lead poisoning. The child's pica had persisted, and it was felt that something definitive had to be done to prevent his ingesting more lead. He chewed on painted wooden surfaces, such as tables, windows, doors, and his toys, and put almost anything in his mouth. From the age of 2 months, shortly after he was weaned from breast to bottle, until the age of 27 months, he had lived with his grandmother. He had not seen his parents during the period of separation. The pica started soon after he left his grandmother and returned to his parents. He was described as quite passive for a long time after his return to his parents, being unable to ask for anything. He had difficulty in handling frustrations and in expressing aggression in relation to his mother. There were elements of neglect and lack of attention from the mother. At the time of the examination part of the child's behavior could have well been reflecting organic elements of the encephalopathy. The hyperactivity, lack of ability to control aggression in general, impulsivity, and distractibility were all suggestive of an organic process. Subsequently

he has been hospitalized with convulsive seizures. He seemed to focus on mouth activities. The pica may have represented an attempt to recreate a more satisfying period early in his life in which the mouth activities were prominent.

The child and parents were seen in therapy over a period of eight months. The parents were helped to handle their guilt about the separation from him in early life and to give up their pushing and controlling him in the direction of independence. Rather, they were encouraged to accept his periodically wanting to act and be taken care of like his baby sister. The boy was helped to be more comfortable with his own hostile and retaliatory urges resulting from his being frustrated. In the process of treatment it was learned the boy was using his eating of paint not only as a means of obtaining oral satisfactions, but that his pica had acquired an aggressive meaning for him. Long after he had given up his pica, he told his mother when a demand of his had been refused, "If you don't help me, I'll eat paint."

COMMENT

When lead poisoning is due to pica, there are other factors than plumbism alone involved. These factors, which may be continuing to operate when the child goes home, are (1) disturbances in the relationship between the mother and child, (2) organic brain damage, and (3) economic and cultural factors. That pica is the primary cause of lead poisoning in children has been reported by numerous authors for some time.* The observations of these six cases confirm this.

For the most part, previous discussions of the causes of pica have been brief and descriptive, without attempts to understand pica in terms of what is going on between the child and his parents. Mellins and Jenkins [5] have recently pointed out the need for study of the mother-child relationship in order to understand the psychodynamics contributing to pica or other behavioral abnormalities. Only one study of pica, in a 7-year-old boy by van der Sar and Waszink,[6] dealt with the emotional disturbance. These authors pointed out the need for accurate and exhaustive studies of the emotional aspects of pica, as has been done in anorexia nervosa, in order to give us better insight into the genesis of pica. The present study would also indicate that the physician needs to look further into the details of the child's relationships and environment. For corrective measures in such problems, the physician may need to send the family to a social agency, a child guidance clinic, or a medical social worker for specialized help.

That there are economic and cultural factors operating which necessitate families' living in property in poor repair was evident in this study. Four of the six children ate loose plaster or peeling paint. Another child chewed paint from a second-hand crib which was refinished with lead paint. The cultural standards of child care were also lax.

Four of the six children in this study were given psychological tests, and all four of them showed evidence of some organic brain damage. It is uncertain whether all the damage was due to lead, or whether (particularly in two of the cases) it may have preceded and contributed to the pica. One child was premature and the other a difficult breech delivery. It is known that organically damaged or retarded children need more help from their parents than the average child. Where these increased dependency needs were not met, the children seem to have persisted in mouth activities for satisfactions. If this were not true in these cases before the lead encephalitis, it was certainly true after it, since clinical evidence of organic brain damage was present in all the patients studied. Thus the very factor that started the pica in the first place, i. e., the distorted mother-child relationship, was put under even greater strain in terms of the increased need of the child. This is therefore a most compelling reason to expect the persistence of the abnormal appetite if skilled help is not provided to deal with the distorted dependency pattern. As was seen, the mouth was used as an accessory sense organ where there was brain damage resulting in perceptual impairment. At the time of examination of these children, it could only be speculated whether part of the organic damage found had preceded and contributed to the pica or was all a result of damage by the lead ingested. Byers and Lord [7] have

* References 2-4.

studied 20 children who had lead poisoning and found impairment of the learning process in all but one.

The most important and consistent factor in pica, to which the other factors were contributory, was the mother-child relationship. Several points in the relationship that were important in these six cases were (1) the mother encouraged the child's excessive oral activities, (2) there were significant separations from the mother, or (3) the mother had emotional problems which interfered with a good mother-child relationship.

Three of the children, Cases 1, 2, and 3, were encouraged by their mothers toward continuing mouth activities beyond the usual age. Either because they were in sympathy with the child's continuing his oral activities, or because of their own passivity, they found this the easiest way to handle the child when he was upset. There must have been many times when the child wanted a personal response from the mother, but was given instead a bottle to put in his mouth. This sort of pattern can become fixated by reinforcing the use of mouth activities as a substitute for relationship satisfactions.

Two of the children, Cases 3 and 6, were separated from the mothering person just prior to the onset of pica, and in these children, the pica may have been partly a response to separation anxiety on the basis of regression.

The mother of the children in Cases 4 and 5 handled her children rigidly and punitively in terms of denying bodily satisfactions from an early age, and she did not differentiate them in terms of their particular needs at the time. She and the mother of the child in Case 2 stated they did not want to "spoil" their children. Their children were described as children who became disturbed at times when people tried to relate to them.

The mothers presented quite varied pictures in terms of intelligence and manifest personality characteristics. Two of the mothers were below average in intelligence, but the others were apparently at least average. However, all of the women were found to be immature and to be disturbed in interpersonal relationships. At least four of them were preoccupied with satisfaction of their own dependency needs to the point where they were unable to express warmth toward others except as others were considered to be extensions of themselves. All displayed strong hostile drives, with four of the mothers showing passive-aggressive trends and one expressing her aggression more openly and punitively. All of the mothers were somewhat insecure and anxious, with all using repression and avoidance to an excessive degree as defenses. Two of the mothers were rigid, pushing, and controlling; three were passively conforming; two made extensive use of denial as a defense. Although they were urged to bring the children to medical clinic for follow-up, half of the mothers neglected to bring them back.

From these six cases, it appears that a child may turn to excessive mouth activities if his normal dependent needs for satisfactions in early relationships are not met. Mishandling of the child may lead to the child's remaining in the early pattern of mother-child relationship, where the focus is on mouth activities. This pattern is similar to that of addiction to alcohol or drugs in adults. Fenichel [8] points out that it is the striving for security combined with the desire for satisfaction (in this study, from the mouth) that characterizes the irresistible impulses, among which he includes the addictions. Children with pica might be considered addicts to their pica, if they are beyond the age when it is normal for them to repeatedly put things in their mouths.

SUMMARY AND CONCLUSIONS

Six cases of lead poisoning have been studied. We realize that this is too small a number of cases on which to base definitive conclusions, but feel that the study of these six cases indicates the areas in which we need to do more intensive study in order to further our understanding of pica.

All six of the children had ingested lead as a result of pica. Although the normal

behavior pattern for mouth-object activities in children begins at 6 months and disappears at 12 months, this pattern may persist longer in retarded or organically damaged children.

Psychiatric study of the children and their mothers has shown several factors in the early relationships that have contributed to the pica. These are (1) encouragement by the mother of the child's excessive oral activities rather than her response to the child in a more personal relationship with him, (2) significant separations of the child from the mother, or (3) emotional problems of the mother which interfered with a good mother-child relationship. Economic and cultural factors, as well as factors of organic brain damage, also contributed.

This study indicates that the physician needs to look further into the details of a child's relationships and environment in order to prevent further ingestion of lead-containing substances. For corrective measures, the physician may need to send the family for specialized help such as is available at a social agency, child guidance clinic, or medical social service department.

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C-Reactive Protein in the Acute Phase of the Common Contagious Diseases

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Although C-reactive protein has been known for more than 20 years, general interest in it is of more recent date. This abnormal protein occurs in the blood of patients during the acute phase of certain diseases. It reacts with the C-carbohydrate of the Pneumococcus and was originally found in studies of patients with pneumonia.

A number of investigators have studied the occurrence of C-reactive protein in the serum of patients with rheumatic fever. The other infectious diseases have been less well studied.* Papers have appeared dealing with tuberculosis,[5] viral hepatitis,[6] and allergy.[8]

The common diseases of childhood present a group of inflammations in which the occurrence of C-reactive protein (CRP) might be expected. As this is a quick and simple test which might well be useful in diagnosis and treatment, a survey was carried out on patients at Willard Parker Hospital. Not all of these patients were children, as during this period many adults were admitted with infectious fevers.

MATERIALS AND METHODS

Dr. Harrison F. Wood, of the Rockefeller Institute, supplied us with antisera prepared in rabbits in his laboratory. The antigen used was purified C-reactive protein obtained from ascitic fluid.

A rack with Plasticine-lined base, like those used for capillary precipitation tests, was used for this investigation. The capillary tubes were 56×1 mm. internal diameter and were autoclaved before use. Blood samples were collected as clotted specimens, usually taken on the first hospital day but occasionally taken on the second day. Some sera were tested both before and after inactivation at 56 C for 30 minutes. This is the procedure used in routine serology testing, and we were interested in discovering whether such sera could be used for the test.

A capillary tube is inserted into the C-reactive protein antiserum, and approximately 1 in. of serum is allowed to flow up the tube. Without allowing an air bubble between the two sera, the same tube is inserted into the serum to be tested and a similar amount is collected in the tube. The tube is shaken and inserted into the Plasticine with an air space of ½ in. at the bottom. A rack of several tubes is incubated at 36 C for two hours. They are then placed in the refrigerator at 4 C overnight, and readings are made using a strong light against a dark background. The precipitate is measured in millimeters. Positive results are expressed in the number of millimeters of precipitate, followed by a plus sign, e. g., 3+ and 5+. Eight plus is a maximum reading. Tubes are used once and are discarded.

RESULTS

The Accuracy of the Test.—Eighty-two sera were tested repeatedly at weekly intervals from three to eight times. No variation greater than ±1 mm. was noted in any case, with the exception of two specimens which showed bacterial contamination.

The Use of Inactivated Serum.—In 100 cases serum from a variety of infectious diseases was tested when fresh and later when inactivation had been carried out, as described above. In no case was there any variation greater than ±1 mm. between the

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* References 1-4.

reading before and the reading after inactivation. It has been shown, however, by others [7] that heating above 65 C will destroy the CRP.

The C-Reactive Protein in Patients with Acute Fevers.—The sera in 298 cases in the acute phase of illness were tested for CRP. The results of these tests are shown in Table 1. It is to be noted that in approximately half the cases the test is negative. Ash found 68% of a series of tuberculous patients positive.[1] Using pneumococci to show nonspecific capsular-swelling substance (analogous to CRP), Lofstom [2] found only 23 of 54 patients with pulmonary tuberculosis who had a positive result, which is very close to our result. However, the sera of his patients with scarlet fever were much less frequently positive than ours were. This requires further investigation with a larger series of patients. Havens and co-workers [6] and Hedlund [3] agree that the test for CRP is rarely positive in viral hepatitis. It is unlikely that the test for CRP will be of any help in the diagnosis of any of these diseases, but it may be of assistance in following their course. The occurrence of a contagious disease during active rheumatic fever will interfere with the usefulness of the CRP test in the management of these patients, but this is equally true of the sedimentation rate.

TABLE 1.—*C-Reactive Protein Readings in Various Infections*

	Cases, No.	Mean, Mm.	% Positive	Cases with Each Reading, No.						
				0	1+	2+	3+	4+	5+	6+
Mumps, uncomplicated	51	2.45	72.7	11	3	7	16	11	2	1
Mumps with orchitis	25	2.52	84.0	4	0	6	9	6	0	0
Poliomyelitis	14	0.86	57.1	6	4	4	0	0	0	0
Varicella	79	2.32	86.1	11	7	20	27	14	0	0
Pertussis	9	0.33	33.3	6	3	0	0	0	0	0
Rubella	44	1.02	45.5	24	7	4	6	3	0	0
Pulmonary tuberculosis	43	1.13	48.8	22	5	7	6	3	0	0
Measles	12	1.83	58.3	5	0	0	6	1	0	0
Scarlet fever	8	2.00	87.5	1	1	4	1	1	0	0
Acute tonsillitis	13	2.61	92.3	1	3	1	3	5	0	0
Normal subjects*	36	0.19	19.3	29	7	0	0	0	0	0

* These normal subjects were members of the staff of an infectious disease hospital. They were carrying out their normal duties, but were not questioned closely regarding minor ailments.

TABLE 2.—*C-Reactive Protein Readings Followed in Some of the Patients Included in Table 1*

Diagnosis	Hospital Day							
	1	2	3	4	5	6	7	8
Varicella 1	3+	...	0	0	...	...	...	...
Varicella 2	...	2+	...	...	...	...	...	0
Varicella 3	...	...	4+	3+	...	0	...	...
Varicella 4	...	...	4+	...	4+	...	2+	...
Mumps with orchitis 1	4+	3+	...	0	0	...	...	...
Mumps with orchitis 2	3+	4+	3+	2+	...	0	...	...

CRP in varying amount, however, can occur in all the diseases tested. The results of this test in normal persons are also shown in the same Table.

A few cases were followed on consecutive days, and the results of these tests are shown in Table 2. This shows that the amount of CRP parallels the activity of the disease process.

COMMENT

We found less CRP in patients with active tuberculosis than Shetlar and co-workers,[5] who found the test positive in 23 of 24 cases.

In our 36 normal persons values over 1+ were not found.

SUMMARY

Serum samples from 298 cases of common contagious diseases in the acute stage were tested for C-reactive protein.

In all the diseases tested C-reactive protein occurs in a proportion of the cases.

The activity of some of these diseases has been shown to be paralleled by the amount of C-reactive protein in the serum.

The test is oftenest positive in acute tonsillitis, scarlet fever, varicella, and mumps.

Serum samples which have been inactivated at 56 C for 30 minutes can be used for the test.

Serum can be stored at 4 C for several weeks before testing.

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The Parent-Child Relationship and the Physician

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Modern concepts of personality development stress the important role of the parent-child relationship in guiding the psychological growth of the child into healthy or unhealthy channels. So much has this been stressed that it may be taken for a self-evident truism, with no appreciation of its profound implications, or it may be exalted to the alpha and omega of psychiatry. Precisely because the role of the parents is being stressed in this paper, it is necessary to emphasize at the outset that it should not be regarded as the sole determinant of the child's behavior. It is one important factor among many: the endowment of the child, his physical health, the social condition of his family, cultural patterns, the status of schools in the community, and so on, which have been discussed in a previous communication.[1] The relationship between parent and child must always be seen against the background of the social setting in which it occurs.

The importance of this relationship, however, can be seen clearly from a consideration of the process of psychological development. Man is a social animal. The infant's structural endowment makes his evolution into a human being possible, but he develops specfic human characteristics only in the presence of a suitable social environment. Severely deprived infants may not survive the neonatal period * or may show marked and apparently irreversible developmental lag.†

Even characteristics as "biological" as vision and tactile perception become functionally useful to the organism only via the learning process.‡ If this be true for such attributes, certainly the social characteristics of the child, language development, aspiration levels, and community adjustment are, even more emphatically, learned patterns of behavior. Recent work of fundamental importance has indicated the cultural basis for masculine and feminine "traits" commonly assumed to be biologically determined.§ To hypothesize innate aggressive instincts,[11] for example, because aggressive behavior characterizes a culture, is to engage in circular reasoning on the supposition that what is, must be. Other cultures are known in which hostile acts of one man or group of men against another are unknown and unthinkable.[12] It is clearly the experience provided for our children that builds into them the attributes demanded by our culture.

From this vantage point the family may be regarded as the "carrier" of the culture. The child spends his first few years almost entirely within the family circle and a major, though gradually declining, portion of his youth within its limits. The child's growth, dependent as it is upon what is supplied from without, thus cannot but be influenced in a significant fashion by the psychological atmosphere of his home. Consequently, pathological distortions in intrafamilial relationships can be expected to have not only

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* References 2 and 3.

† References 4, 5, and 6.

‡ References 7 and 8.

§ References 9 and 10.

immediate but also far-reaching influence upon the course of the child's development.

It is this important implication of modern psychodynamic theory for preventive psychiatry that has as yet been insufficiently understood. In the task of mental hygiene—the task of maintaining good mental health and preventing mental illness—the pediatrician and physician occupy key positions. Prophylactic psychiatry is as properly their province as is immunization or periodic physical examination.

The strategic role of the family physician is evident from the following considerations. First of all, it is he who is consulted about day-to-day problems of development, and it is his advice that is sought when more serious deviations of behavior appear. But even more important from the preventive standpoint is the fact that he is in a position to detect unhealthy trends which the family may not recognize as disturbing. A thorough medical history should include under "System Review" the category "Emotional and Intellectual Development," under which the physician inquires about the child's school adjustment, his friends, his relationship to his parents, his eating and sleeping patterns, and so on. Moreover, observation of the child's behavior in the waiting room and his response to the physical examination provides important information about his adjustment. Finally, home visits are apt to be particularly informative, as the physician observes where the family lives and how they live together as a unit. If alert to the psychological significance of the data which his medical practice supplies in abundant detail, the physician has a basis for making a sound preliminary psychiatric evaluation.

When the physician or pediatrician is consulted about behavior that concerns the parents, it is useful for him to ask himself two questions: Is the concern expressed by the parents appropriate to the problem the child presents? Just what has caused the parents to seek help at this moment?

The first question, Is the concern appropriate? brings the problem into focus as a dynamic interpersonal situation and provides clues as to therapeutic possibilities. Excessive concern over normal or near-normal behavior points at once to a problem in parental expectations. It directs the physician's curiosity to the source and development of parental standards in terms of the parent's past and current life experience. Undue agitation over experimental sexual behavior by the child, for example, will often occur against a background of poor marital adjustment, or where there is a history of deviant sexual behavior in one parent or his family which leads to feelings of guilt, and fear that the pattern may repeat itself in the child. Simple reassurance as to the normalcy of the child's behavior will usually not be effective unless the parents can be sympathetically encouraged to give voice to their own latent attitudes. The severity of the problems uncovered will dictate whether more help will be required than the family physician is prepared to offer.

An 8-year-old girl was brought to the family physician by a mother agitated by her daughter's confession that she had engaged in sex play with a schoolmate. After the situation had been fully explored and determined to be innocuous, tactful questioning elicited a tearful history from the mother of a repressive sexual upbringing, sexual maladjustment in marriage, and fear lest the daughter have a similar difficulty. It was this that had led the mother to react to the incident by flooding the child with "sex education" to the point where this rather bright youngster embarrassed her father by discussing sex rather explicitly during dinner hour and, on the occasion, by innocently asking that he show her how he was made. Within the limits of one consultation, a family crisis that could indeed have been upsetting to all family members was averted. Mother was reassured that, while the behavior in question was normal, it nevertheless could be gently discouraged without dire consequence. Furthermore, it was pointed out rather forcefully that a healthy attitude toward sex in the household did not include family exhibitionism. The mother was encouraged to discuss her own rather specific

sexual dissatisfactions with her husband, and the physician offered to speak to him as well, an offer that was gratefully accepted.

On the other hand, one may observe that the parents express concern over a relatively unimportant feature of the child's difficulties while they remain apparently oblivious to severe psychopathology. For instance, the complaint may be that of poor school progress, when the major issue is extremely disturbed behavior. This gives an immediate clue as to the dynamics of the problem as well as a measure of the difficulties that therapeutic efforts will have to overcome. A marked disparity between what bothers the parents and what is wrong with the child, in general, suggests a very difficult and deep-seated problem. It will be a major victory if the family physician can help the parents to see the problem for what it is and prepare them to accept psychiatric referral.

The second question, Why is help sought now? sharpens the insights provided by the first. The patient may have been stealing for years, when suddenly the parents insist upon immediate professional advice. A careful history will elicit the fact that a threat of action by school or court authorities is behind the sudden "awakening" of concern. This alerts one at once to the question of parental attitude toward the child's antisocial behavior. Is it, one will wonder, being covertly encouraged? This raises considerable doubt as to the adequacy of the motivation for help. In another instance, the first visit after many years of poor adjustment will be precipitated by the emergence of behavior that is intolerable to the parent, though it may be a sign of healthy potential in the child. A 12-year-old boy had been an unhappy and almost friendless child but one who had mechanically executed his father's endless demands. It was only when he began to rebel by failing in his school work, despite an excellent I. Q., and by doing poorly in the music, dancing, and elocution lessons forced on the child that his father frantically sought guidance. As the physician was able to point out to the father in a factual, noncritical fashion how much of his son's initiative he had usurped, the father expressed his own frustrated ambitions that he had sought to realize through the son. When the father, by virtue of the physician's specific guidance, withdrew his overprotective control, the boy was able to assert his own personality in a positive way by assuming responsibility for his own behavior.

The case illustrations cited thus far have centered about the evaluation of problems brought to the office as *problems*. The psychiatrically oriented physician may, in addition, during the course of routine office visits, note unhealthy features in the relation between parent and child of which neither may be fully aware and which, in any event, are not brought out as problems in need of solution. In one respect, this makes the task more difficult, since the "nuisance value" of symptomatic complaints is a powerful motivating force for change. At the same time, however, the trends are likely to be less inspissated and parents and child more responsive to suggested change if properly presented.

In general, psychological guidance, even in situations where problems are not particularly severe, is not merely a matter of dispensing wise maxims of child care as one might dispense medication. An essential ingredient is the provision of an outlet for the parent to give vent to his own pent-up feelings. This at the same time sharpens the physician's insight into the problem and indicates to him the role he should play and the amount and kind of advice he may safely give.

This situation is not unparalleled in medical practice. The analogy suggests itself between advice on child rearing and dietary planning with a patient. There is no one right diet or way to eat. One knows most of the essential nutrients and knows as well that many different forms of cookery will supply these nutrients. This dietary relativism does not mean that all diets are equally good, for we know that certain diets are notoriously deficient and give rise to pellagra, beriberi, hypoproteinemia, etc. One then tries to insure that what the patient

eats will supply his special nutritional needs —if he is obese, diabetic, adolescent, anemic, or whatever—but he will present the diet in the form of foods prepared in the way traditional for the patient's family.

Similarly, there is no one right way of child rearing, no matter what the popular "experts" would have us believe. There are many acceptable ways that will be more or less comfortable for particular parents, but there are also many ways that are grossly inadequate. In counseling with the parent, one takes into account the psychological needs of the growing child and then tries to guide the parents to meet those needs within the traditional framework of his own culture and with respect, it should be added, to his own needs as a person.

There are problems that are largely attributable to ignorance—ignorance on the part of the parent as to what children are and how they may be expected to behave. One thinks in particular of the young mother and her newborn child. Anxiety can distort what should be a happy experience for both into a tense and mutually frustrating existence. A good many exasperating telephone calls to the family physician over nonexistent problems can be obviated if the interminable cycle of maternal anxiety and physiological instability in the infant is interrupted by allowing the mother to verbalize her own fears, helping her to see how these are related to her uncertainty over her own adequacy and role, and by supporting her, if need be, against the professional grandmothers who stand by clucking their tongues in disapproval.

To speak of unrealistic parental expectations implies a disproportion between parental standards and the child's performance. Normal standards are unrealistic if applied to developmentally subnormal children. The slow child, beleaguered and beset by badgering demands, told constantly by teacher and parent, "You could if you would," will be disturbed as well as retarded; early recognition and sound advice, based upon an understanding of the child's needs, enable the same child to become a source of pleasure rather than dismay.

A final pattern of difficulty commonly seen is that caused by projection onto the child of difficulties in the marriage. This is often expressed in cyclic patterns of overindulgence and episodic uncontrolled anger. The child is resented as the embodiment of a miserable marriage and the barrier to a divorce; guilt over this undeserved hostility leads to an inability to exert normal discipline until his behavior becomes intolerable, and then hell breaks loose, to be succeeded almost at once by an overindulgence as the parent genuinely regrets his angry outburst. Or one may hear hypercritical and vindictive attitudes expressed toward the child. The venom of these attacks becomes less inexplicable when one hears the parent say, "He's just like his father!" or "She's the image of that damn sister-in-law of mine who's ruined our marriage." In such situations, admonitions not to punish or overindulge the child are quite useless; the parents in most instances know already that they are behaving inadequately and feel guilty. The problem must be tackled on quite another level and will require referral for specialized help in the form of marriage counseling, legal advice, or psychiatric treatment.

This paper has attempted to stress the responsibility of the family physician in the maintenance of mental health and the contribution he can make by employing the skills and knowledge he already has at hand. Psychiatrists are not now, nor are they ever likely to be, available in sufficient number to handle the bulk of the interpersonal problems that arise in the course of our complex and rapidly changing civilization. The psychiatrist's role is, and should be, limited to those problems of sufficient severity to require time, effort, and specialized knowledge beyond the limitations imposed by the demands of general practice.

What is required, above all, to help troubled children and their parents is sincere interest and a willingness to listen; a faith in the ability of most people, given

a chance, to work out their own solutions, and reasonable confidence, without arrogance, in one's own judgment. These fundamental attributes are enhanced and made more useful by the acquisition of specialized knowledge incorporating the wisdom of broad experience and conceptual clarity.[13] The scope of the problem of mental illness demands that the family physician attend to it as zealously as he does to other endemic and epidemic ills. The practice of medicine must be geared to the treatment of the "compleat patient"; the one "compleat physician" capable of assuming this responsibility is the family physician.

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News and Comment

ANNOUNCEMENTS

Residency in Pediatric Oncology.—Applications for the residency from Jan. 1, 1957, to Dec. 31, 1957, in Pediatric Oncology at Memorial Center for Cancer and Allied Diseases in New York will be received up to April 15, 1956. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3600 annually plus maintenance. For application forms and information write Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York 21.

Case Reports

RHEUMATOID SPONDYLITIS IN A PREPUBERTAL FEMALE

T. N. LYNN, M.D., St. Louis

RHEUMATOID spondylitis has been known by many names in the past, among them rhyzomelic spondylitis, Marie-Strümpell's disease, von Bechterew's syndrome, ankylosing spondylitis, spondylitis deformans, and atrophic spondylitis.[3]

This is generally considered to be a disease of young adult males, the age of onset in the vast majority of cases occurring between 15 and 40 years of age.[3] The disease occurs predominantly in males, with the sex ratio usually reported as 10:1,* though varying in extremes from 4:1 to 20:1.†

A review of the literature reveals a striking paucity of reports of the development of this disease in prepubertal girls. Tyson and co-workers,[16] in a 20-year study of the rheumatoid spondylitis patients seen at the Presbyterian and New York Orthopedic Hospitals, stated that the youngest age of onset seen in girls was 14 years. No statement was made regarding the correlation with puberty. Polley and Slocumb ‡ found in a series of 1018 cases, in which the age of onset could be established, that there was one case in a girl under 13 years of age and presumably prepubertal. Other authors § have testified to the relative rarity of the disease in prepubertal girls, and Turney,[15] in 1952, expressed doubt that rheumatoid spondylitis ever occurred before the age of puberty. Nevertheless, Lucchesi and Lucchesi [5] reported in 1950 that in their private practice there were 11 cases in girls between the ages of 1 and 10 years. However, no case reports on the girls were given, and it was stated that, among these girls, there were no radiological changes of the sacroiliac joints (considered by most observers to be of primary diagnostic significance).‖

Because of the rarity of the finding of documented rheumatoid spondylitis in prepubertal girls, it seems worth while to report such a case.

REPORT OF CASE

A 14-year-old white girl was seen in the outpatient clinics of the University of Oklahoma Hospitals, complaining of progressive pain and stiffness in her midback and a gradually increasing flexion deformity of her spine of two years' dura-

Submitted for publication June 29, 1955.

* References 2, 6, and 1.

† References 1 and 2.

‡ Polley, H. F.: Personal communication to the author. Reference 9.

§ References 4 to 8.

‖ References 3 and 10.

Figure 1

Figure 2

Figure 4

tion. There was no antecedent history of trauma, neurological disease, or tuberculosis. Physical examination revealed a pale white girl, 50 in. tall, weighing 58 lb., who appeared to be about 9 years of age. A marked "C" type flexion deformity of the spine was present, with the apex of the curve at the 11th and 12th dorsal vertebrae (Figs. 1 and 2). Tenderness was elicited by pressure over the four lower thoracic and the first lumbar vertebrae, and attempted motion of the midback resulted in pain in this area. There was a forward thrust of the neck, but motion in the cervical spine was essentially normal. Chest expansion was restricted to 0.5 cm., measured below the breasts, and post-tussive rales were present in both lung bases. No pain, tenderness, stiffness, or deformity

Figure 3

was present in any joints except those of the spine, and there was no evidence of rheumatic involvement of the eyes, skin, or heart.

Roentgenograms of the pelvis were interpreted as showing sclerosis and narrowing of the sacroiliac joints (Fig. 3). Films of the spine demonstrated the "C" type kyphosis, moderate osteoporosis, and a definite squaring of the anterior border of the fourth lumbar vertebra (Fig. 4). Films of the peripheral bones and joints showed generalized osteoporosis but no evidence of arthritic change.

The laboratory data revealed the hemoglobin to be 11.2 gm. per 100 cc., the white blood cell count to be 7300 per cubic millimeter, and the erythrocyte sedimentation rate to be 52 mm. in one hour (Wintrobe). The C-reactive protein was 3+, the antistreptolysin O titer was 125 units, and the sheep-cell hemagglutination test [17] was positive in a dilution of 1:56. The total serum protein was 9.03 gm. per 100 cc., with an albumin-globulin ratio [7] of 3.61:5.42. The protein-polysaccharide ratio [12] was 2.54.

The therapy was 150 r of x-rays per week for four weeks, delivered to the lumbodorsal spine with shielding to prevent damage to ovarian tissue. Marked subjective improvement in back pain was noted before completion of therapy.

COMMENT

The earliest radiological signs of rheumatoid spondylitis occur in the sacroiliac joints and consist of marginal decalcification and indistinctness progressing to marginal osteosclerosis and finally to loss of the joint space. Changes in the apophyseal joints are similar to those seen in the sacroiliac joints. Early changes seen in the vertebral bodies are a squaring of the anterior borders and later pointing of the corners of the bodies, both due to calcification in the anterior longitudinal ligament. This ligamentary calcification progresses to bridging between the vertebrae, and the pathognomonic bamboo spine results.[10]

The case presented is from both a clinical and a radiographic standpoint unequivocally one of rheumatoid spondylitis; certain of the serological studies, however, vary somewhat from the expected. The sheep-cell hemagglutination test, first described by Rose and co-workers [11] in 1948 and later modified by Ziff, is a procedure in which a unique heterophilagglutinin for sheep cells can be demonstrated to be present in the sera of a great number of patients afflicted with one of the collagen diseases. Ziff and co-workers [17] found this test to be highly specific for rheumatoid arthritis and obtained negative results on a series of 11 rheumatoid spondylitis patients. However, Shetlar and Payne ¶ have found a significant number of positive reactions among rheumatoid spondylitis patients. The protein-polysaccharide ratio is a value obtained from the determination of the total serum protein and the serum polysaccharide level. This ratio is elevated in certain diseases involving connective tissue, including rheumatoid arthritis, gout, disseminated lupus erythematosus, and some cases of rheumatoid spondylitis. Shetlar and co-workers,[18] in a series of 13 patients, found a range of 1.52 to 2.29. The value of 2.54 obtained in this case represents an extension of this range.

SUMMARY

The reported occurrence of rheumatoid spondylitis in young adult females is briefly discussed, and a single documented instance of this disease developing in a prepubertal girl is cited as found in a review of the literature. A second case occurring in a prepubertal girl is reported.

Barnes Hospital.

¶ Shetlar, M. R., and Payne, R. W.: Personal comunication to the author.

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News and Comment

ANNOUNCEMENTS

Congress of the Pan American Medical Association.—The next and Tenth Inter-American Congress of the Pan American Medical Association will be held in Mexico City. The scientific sessions will be held April 15-21, 1957, at 9 a.m. The congress will be held in sections, covering all branches of medicine and surgery. There will be medical moving pictures, panel discussions, and scientific and technical exhibits. The Association has 42 medical sections, including the new "Section of General Practice."

Four days will be devoted to scientific sessions, and the next three days will be spent in sightseeing, with visits to Cuernavaca, Taxco, and Acapulco. Monday and Tuesday of the following week, medical meetings will be held in Guatemala City in conjunction with our local chapter there.

A large number of physicians are expected to attend from all of the Latin American countries as well as from the United States and Canada.

The President of the Association is Dr. Pedro A. Gutiérrez Alfaro, Minister of Sanitation and Public Welfare of Venezuela, and the Executive Director is Dr. Joseph J. Eller, 745 Fifth Ave., New York.

Fellowships in Pediatric Cardiology.—One or two fellowships in pediatric cardiology will be available beginning July, 1956, at The Children's Orthopedic Hospital, Seattle. Training will be in conjunction with the Department of Pediatric Cardiology, University of Washington School of Medicine. Salary open. Desire applicants with minimum of two years of pediatrics. Direct correspondence to Robert A. Tidwell, M.D., The Children's Orthopedic Hospital, 4800 Sand Point Way, Seattle 5.

SPONTANEOUS RUPTURE OF THE STOMACH IN THE NEWBORN

WILLIAM B. KIESEWETTER, M.D., Pittsburgh

FOUR NEWBORN children were admitted to the surgical service at the Children's Hospital of Philadelphia in a four-year period with the unusual finding of a spontaneous perforation of the stomach. Our interest in the problem was aroused, and it is our purpose here to record briefly the case histories on each of these patients, bring the literature up to date as to the occurrence of this lesion, and discuss possible etiological mechanisms by which it can occur.

REPORT OF CASES

CASE 1.—This 5-day-old Negro boy was admitted to the Children's Hospital of Philadelphia with a history that he had had an uneventful birth on Dec. 9, 1949, and had seemed perfectly normal for the first two days of life. On the evening of Dec. 11, 1949, it was noted that the baby was listless, refused his bottle, and became cyanotic, necessitating the use of oxygen. Next morning the respirations were shallow, and the baby continued to be listless with no muscle tone and was unable to support his head. During the morning the infant had a generalized tonic and clonic convulsion, followed during the day by intermittent convulsions of the same sort. On the fourth day of life (Dec. 13, 1949), his condition appeared improved with good color in oxygen and an absence of convulsions. At noon, however, his abdomen suddenly became distended, following which a right inguinal hernia appeared. He also had a bout of hematemesis with subsequent rapid respirations and an ashen gray color. No peristalsis could be heard in the abdomen at that time, and it was noted that the child had some subcutaneous emphysema with crepitation from the right lower abdomen around to the back. The last bowel movement was on Dec. 12, with normal meconium stools having been passed up to that time. He was started on gavage feedings, but his abdominal distention increased although he retained his feedings, and he was transferred to Children's Hospital on the morning of Dec. 14. Physical examination revealed a child in acute distress, who had good color while in oxygen, although his abdomen was tight from obvious distention. No peristalsis could be heard. A supine and erect film of the abdomen revealed a markedly distended gastrointestinal tract, with free air under the diaphragm. With a diagnosis of pneumoperitoneum from ruptured viscus, the child underwent exploratory laparotomy, at which time a large amount of milky fluid was found lying free in the peritoneal cavity, and all of the viscera were matted together with a plastic exudate. There was a 2×2 cm. perforation of the cardiac end of the stomach along the greater curvature. It was a ragged type of gastromalacia, which was debrided and closed in three layers.

The child's immediate response after surgery was remarkably good, considering the amount of contamination which had been present. He was able to be given oral feedings on the third postoperative day but did not show any progressive gain in weight. The child gradually went downhill from what seemed to be a generalized septic process. He finally died on the 15th postoperative day.

Postmortem examination revealed an intact stomach repair but with evidence of massive peritonitis, with some abscesses trapped in the coils of intestine.

CASE 2.—This 2-day-old white boy was admitted to the hospital on Dec. 20, 1952, with a chief complaint of distention of the abdomen. At about 36 hours of age, the child became distended and cyanotic. Feedings by mouth were stopped, and parenteral fluids were begun. The child had had spontaneous bowel movements, but when x-ray examination revealed marked distention of the bowel and pneumoperitoneum, he was referred to the Children's Hospital. He was subjected to exploratory laparotomy, at which time a 1 cm. ragged perforation was found in the midst of a thinned-out stomach wall. A three-layer closure, after debridement of the necrotic area, was carried out. The child got along well for four days following that repair, at the end of which time it became evident that he had pneumoperitoneum again. His abdomen was reexplored. This time he was found to have a perforation in a different area of the stomach. This was apparently successfully closed, because the

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From the Surgical Clinic, Children's Hospital, and the Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia.

child convalesced nicely for a period of 11 days, until Jan. 5, 1953, at which time he suffered a 1-in. wound disruption at the medial aspect of his incision. This proved too much for the child's endurance, although it was closed under local anesthesia. The child never fully recovered and went downhill until his death, on Jan. 7, 1953. At autopsy, he was found to have intact repairs from the preceding surgery, with death due to peritonitis.

CASE 3.—This patient was 2 days of age when she was admitted to Children's Hospital, on Dec. 24, 1952, with the diagnosis of esophageal atresia. The diagnosis had been made at the hospital where the child was born, because she regurgitated her feedings and had several bouts of cyanosis after she was fed. A catheter had been passed, and x-ray examination had revealed that it curled in the esophagus at approximately the level of the third thoracic vertebra. Upon admission, the child had Mongoloid features, but the remainder of the physical examination was negative except for a slight degree of cyanosis. A chest and abdominal film revealed that the child had some right-upper-lobe pneumonia as well as a complete absence of gas in the intestinal tract. With the diagnosis of esophageal atresia without tracheoesophageal fistula, the child was subjected to transpleural thoracotomy on the day of her admission, at which time it was found that the two ends of the esophagus were too far apart to permit primary anastomosis. The upper esophagus was brought out in the neck, and the abdomen was then opened and a segment of jejunum freed from its gastrointestinal continuity. The two pieces of divided jejunum were sewed end to end. The distal end of small intestine was sewed to the stomach, and the proximal portion of it, with attached blood supply, was brought up subcutaneously over the top of the sternum to a point just below the cervical esophagostomy.

Thirty-six hours after the operation, the child was given feedings through the gastrostomy tube, which had been placed at the time of the original operation. She did fairly well on these feedings until the morning of the 10th postoperative day, when a sudden bout of distention took place, with cyanosis and dyspnea. Continous suction was instituted, but it failed to relieve the distention. No bowel sounds were heard, and the child's condition deteriorated rapidly. She died six hours after the onset of the distention.

Postmortem examination revealed a ragged gastromalacia, with a 2 cm. perforation occurring along the greater curvature of the stomach. All suture lines were intact, and the cause of death was judged to be the spontaneous perforation of the stomach.

CASE 4.—This one-day old white boy was born of a first pregnancy of a 43-year-old mother and a 48-year-old father. The child did well for the first 24 hours, with a couple of normal meconium stools, normal color, and only a small amount of distention being present. This distention, however, increased markedly on the second day of life, and the child began to vomit. A flat film of the abdomen revealed a large, distended stomach and duodenum, with free air under the diaphragm. A diagnosis of pneumoperitoneum from ruptured viscus was made, and the child was transferred to the Children's Hospital. Upon admission there, the child was in acute distress. Its Mongoloid facies and markedly protuberant abdomen were the most significant findings. The child was subjected to exploratory laparotomy the same day, at which time a perforation of the lesser curvature of the stomach was found approximately 3 cm. from the diaphragm. This was shaggy and was debrided and oversewn. In addition, there was an atresia of the duodenum found at the ligament of Treitz, and a side-to-side duodenojejunostomy was carried out around the atresia.

The child did well postoperatively for six days, being able to be given oral feedings in 48 hours and actually showing some small amount of gain in weight the last day or two. Suddenly on the morning of the sixth postoperative day the child became listless and somewhat cyanotic and the anterior fontanel seemed to be bulging. A spinal tap was done, and the fluid was seen to contain many actively motile Gram-negative bacilli. The child had been given penicillin and streptomycin and was started on huge doses of tetracycline (Achromycin) and sulfadiazine, but it was to no avail, as he went downhill in the course of the next eight hours and died.

Postmortem examination revealed purulent meningitis to be present as the cause for his death. The intra-abdominal surgery was successful, with normal healing.

LITERATURE

The first large group of patients suffering from spontaneous perforation of the gastrointestinal tract was reported by Elaesser,* in the German literature in 1846. He cited 38 cases of ulcer and perforation of the upper gastrointestinal tract in which there was a high percentage of intracranial disorders. Among this group were seven newborn infants.

Herbut [9] summarized the English literature on spontaneous rupture of the stomach in the newborn in 1943. At that time there were 16 reported cases with only one successfully treated. Since that time 10 addi-

* Cited by Cushing.[3]

Reported Cases of Spontaneous Rupture of Stomach in Newborn Infants

Author	Year	Cases	Survivals
Herbut [9]	1943	16	1
Pendergrass [12]	1946	1	..
Burnett [2]	1947	1	..
Tudor [19]	1950	1	..
Plummer [14]	1950	2	2
Wright [21]	1950	1	..
Ross [16]	1951	2	1
Kellogg [10]	1951	1	1
Beattie [1]	1952	1	1
Greene [6]	1953	2	..
Moncrief [13]	1954	1	1

tional references have been made in the literature to cases of spontaneous rupture, a total of 13 cases being added. This makes the recorded incidence 29 cases, with 7 survivals. These facts are summarized in the Table.

Three of the reports † were of interest and will be discussed below.

COMMENT

There have been a number of attempts to explain spontaneous rupture of the gastrointestinal tract in the newborn infant. The association of intracranial lesions and rupture of the stomach had been noted in the 1840's when Rokitansky ‡ expressed his opinion that there was a neurogenic cause for gastromalacia, ulceration, or perforation in the presence of central nervous system disease. The neurogenic theory held sway until Virchow § stressed that there was a local cause for peptic ulceration or perforation, and by the force of his personality and the authority of his world-wide fame, his thesis supplanted the earlier view. It wasn't until the classic observations of Cushing,[3] in 1932, that the association of intracranial lesions with ulceration or perforation came to the fore again. As a result of three patients with cerebellar tumors dying from perforated stomachs, Cushing delved into the problem quite extensively. He reviewed 11 cases of his own in which there was association between central nervous system pathology and upper gastrointestinal tract hemorrhage and/or perforation. Three of his patients were children. Evidence was also presented that experimental lesions anywhere in the intracranial course of the fibers leading from the anterior hypothalamus to the vagal center would give erosions, ulcers, or perforations of the gastrointestinal tract. Basically, Cushing returned to the neurogenic view as playing a large part in the causation of this pathological entity, working locally through an autonomic discharge. He suggested that the autonomic system caused vasospasm and autodigestion of the gastrointestinal tract by the excess acid working on a locally impaired area.

Russell [17] felt that spontaneous rupture was due to hydrostatic pressure on the intestine at the time of birth. This pressure could not be distributed along the length of the intestine because of a meconium plug or a kink in the tract itself. Therefore rupture was thought to be due to a direct physical force.

Others have felt that there was excessive acidity produced in these children, attributing the cause to this local factor. There are some interesting data which were accumulated by Miller,[11] in which upon the examination of a considerable number of infants, he found that gastric acidity in the newborn child was equal to that of an adult and was maximal at 24 hours of age. It then decreased for approximately nine days, when it began to approach a more normal figure for a child, but still considerably below that of the adult acidity level.

Several interesting pieces of experimental work have appeared in the literature concerning the neurogenic etiology of hemorrhage, ulceration, and perforation. French [5] and his colleagues, in 1952, did a series of experiments upon cats in which they stimulated the hypothalamic areas. By so doing, they were able to produce gastrointestinal hemorrhage in 14 out of 15 cats so stimulated. They felt that this was mediated through the autonomic nervous system, inasmuch as such blocking agents as tetraethylammonium (Etamon) provided a marked degree of prophylactic benefit when given before

† References 8, 14, and 21.

‡ Cited by Cushing.[3]

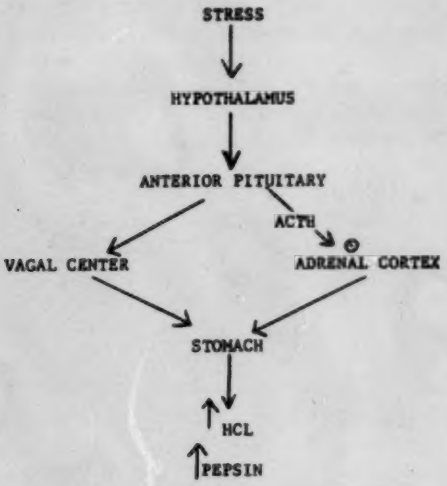
§ Cited by Cushing.[3]

the stimulation. Porter [15] continued this group's work with monkeys and came to the conclusion that there was a dual control over the increased hydrochloric acid resulting from stimulation of the hypothalamic area (1) from the anterior hypothalamus by way of the vagus (he was able to block this effect by doing vagotomies prior to stimulation) and (2) from the posterior hypothalamus through humoral mechanisms by way of the pituitary and adrenal glands. He was able to block this mode of approach by adrenalectomy before stimulation. In 1955, Davis and co-workers [4] drew some conclusions from a review of 7000 neurosurgical cases in which 46 patients had gastrointestinal hemorrhage after surgery. This group felt there was no correlation between the histologic or anatomic extent of the central nervous system lesion and the tendency to gastrointestinal bleeding. They also felt that central nervous system pathology was not a requisite for such bleeding, inasmuch as patients subjected to laminectomy and trigeminal neurectomy also suffered from this problem. They were unable to confirm French's work on the hypothalamic stimulation of cats. In summary, this group felt that the ulcerations and hemorrhage were an extreme pathophysiologic response to the stress of surgery wherever it was carried out. Watson and Netsky [20] feel that there is some recent experimental and clinical reason to suspect that the hypothalamic centers are not solely involved in the production of the gastrointestinal pathology, since cortical and subcortical centers have been found which may have an effect upon the hypothalamic or vagal centers. He thinks that perhaps the cortical centers have a moderating influence on the diencephalon. Removal of such dampening effect may give these centers unbridled activity which can result in ulceration and malacia. He, moreover, feels that a "Cushing ulcer" is not limited to postoperative craniotomy patients, and he cites six cases of his own in which this was true.

With the advent in recent years of our knowledge of the work of the adrenal cortex, there have been some interesting concepts put forth by workers in this field that may well play a part in the over-all picture of perforation of the stomch in the newborn child. Hans Selye [18] states that there are a number of stresses which can produce upper gastrointestinal bleeding. Among them are (1) emotional tension; (2) trauma, especially to the brain; (3) brain tumor; (4) anoxia; (5) burns, and (6) shock. Gray and his associates || express much the same opinion as a result of their experience with corticotropin and cortisone. They cite a number of acute cases of hemorrhage and perforation in patients who were undergoing corticotropin or cortisone therapy for lesions not involving the gastrointestinal tract. These patients were asymptomatic so far as an ulcer history was concerned until the administration of these substances. The activation, hemorrhage from, and perforation of preexisting ulcers was also noted by them. Experimental work was carried out by these invesgators at the Peter Bent Brigham Hospital in which corticotropin was given to normal individuals, following which their gastric hydrochloric acid and pepsin rose into the range of that found in ulcer patients. Cortisone had the same effect. However, corticotropin given to patients with adrenal insufficiency failed to produce this response, suggesting that in addition to the already well-known vagal pathway for hydrochloric acid stimulation there was one mediated through the adrenal cortex. The steroids of this organ have proved to be the mediating mechanism, because cortisone given to the adrenally insufficient patients once again gave the rise in hydrochloric acid and pepsin. Uropepsin was used as the measure of the increased gastric acidity because the pepsin came from the stomach to the kidney and was excreted as uropepsin, and could be used therefore as a quantitative measurement of the degree of stimulation. Some dogs were gastrectomized and the same experimental process carried out with no rise in uropepsin through the administration of cortisone.

|| References 6 and 7.

The same workers found that stimulation of the tracts leading from the anterior pituitary to the vagal medulla centers would result in gastric erosions, accompanied by hyperchlorhydria. Section of the vagus nerves still allowed this to take place, so that it gave further support to the fact that there was in addition to the neurogenic mechanism also a humoral mechanism. They felt that "stress" seemed to cause the anterior hypothalamus to secrete a humoral substance, which caused the pituitary to release corticotropin, which, in turn, caused cortisone to be poured out and to act directly upon the stomach. The two



Dual pathways of stress action on the stomach.

pathways by which this mechanism can work are outlined in the Figure.

One of the interesting elements in reviewing the work of Gray and his collaborators was that they felt that anoxia caused severe stress, and they actually cited two cases where perforation occurred as a result of acute and chronic anoxia. This is of particular interest when one notes that Watson [20] referred to "diencephalon release"—when removal of cortical inhibition allows for hypothalamic overactivity. Anoxia certainly would lessen such cortical control and thus permit the hypothalamic-pituitary-adrenal mechanism to come into play. We were struck with the association between anoxia and spontaneous stomach perforation when we combined the three previously reported instances in the literature ¶ of the last decade with two of our cases (Case 1 and 3), in all of which anoxia was apparently a factor. One of Greene's [8] two patients was anoxic after birth due to a tracheal plug. One of Plummer's [14] two patients had anoxia following convulsions and a five-day febrile episode which eventuated in perforation; this child, however, survived this episode. Wright and Scott [21] cited one case which ended fatally in which there was a much prolonged labor, suggesting that there may have been some anoxia during this period, which played a part in the spontaneous perforation from which the child died. In Case 1 the child had a period of frank cyanosis and convulsions several days before the actual episode of perforation. Case 3 was a child with esophageal atresia, resulting in cyanosis and an impaired respiratory effort. Perhaps all of this points to the possibility that anoxia either during birth or in the neonatal period may be sufficient stress to trigger the adrenal mechanism by which autodigestion of the stomach may take place. In addition, it is an inviting hypothesis that the vasospastic mechanism working locally, which Cushing advocated, may play a secondary role in making the upper gastrointestinal tract prey to this situation. Finally, the cortical steroids are well known for their ability to produce thrombosis. This property in the cortisone elaborated by the stress of anoxia could well contribute to lowering the local resistance of the stomach to the action of the stomach acidity.

SUMMARY

Four cases of spontaneous perforation of the stomach in the newborn period are reported.

Stress of several types, including anoxia during or immediately after birth, is considered as a possible initiating cause for the

¶ References 8, 14, and 21.

hypothalamic-pituitary-adrenal mechanism to come into play with the resultant gastromalacia and perforation.

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News and Comment

ANNOUNCEMENTS

Postgraduate Seminar for Pediatricians.—The fifth annual postgraduate seminar for pediatricians will be conducted at St. Christopher's Hospital for Children, Philadelphia, by the Department of Pediatrics of Temple University School of Medicine, from May 16 to 19, inclusive.

Sessions will be devoted to problems in the fields of pediatric hematology, cardiology, surgery, endocrinology, psychiatry, neurology, infectious diseases, pathology, and the like.

For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 33.

Progress in Pediatrics

DIFFERENTIAL DIAGNOSIS OF TUMORS AND TUMOR-LIKE LESIONS OF LIVER IN INFANCY AND CHILDHOOD

HUGH A. EDMONDSON, M.D., Los Angeles

INTRODUCTION

TUMORS of the liver in infants and children are rare. When encountered by the clinician and pathologist, they provide problems in diagnosis as well as management. There are few sources of information regarding the general problem of liver tumors in infants and children and their surgical treatment.* The literature deals primarily with case reports or at most with reviews of specific tumors. An unusual opportunity for the study of this group of tumors was afforded incidental to the compilation of material from widely separate sources in preparation of the fascicle on tumors of the liver and intrahepatic bile ducts for the Armed Forces Institute of Pathology.

CLINICAL DIAGNOSIS

The tumors are found in the main in patients under 2 years of age, and an abdominal mass noted either by the parents or physician constitutes the commonest initial finding. The mass is usually noted on the right side of the abdomen and ordinarily moves on respiration. Occasional tumors may arise in the left lobe, and these may be palpable in the epigastrium or even in the left upper quadrant. Both anteroposterior and lateral views of the abdomen may be of help in localizing the tumor in the liver. Primary tumors and tumor-like lesions of the liver often cause a round or oval shadow that projects downward from the right lobe. Extrahepatic neoplasms, such as Wilms' tumor of the kidney and neuroblastoma of the adrenal, have to be considered in the differential diagnosis. Pyelograms usually, but not always, serve to differentiate Wilms' tumor. Neuroblastomas may be more diffiuclt to distinguish from primary tumors of the liver, but roentgenograms disclose that they tend to displace the kidney down and laterally, calcification is frequently present in the adrenal region, and metastases to bone are common.[6] Occasionally the kidney may be pushed anteriorly or even medially.

In patients with a large tumor of the liver the pyelogram may disclose some degree of compression of the right renal pelvis or its possible displacement toward the midline. Barium studies of the gastrointestinal tract have in several instances shown that liver tumors produce external pressure on some portion of the ascending or transverse colon and less frequently on the stomach and duodenum. Tumors of the left lobe may cause external pressure on the stomach only. Hofmann,[4] in 1902, first called attention to the observation that liver tumors tend to displace the colon downward and to the left, while renal tumors push the colon forward. Repeated published reports of liver tumors have substantiated the truth of this finding. Although most of the malignant tumors of the liver in infants and children metastasize late in the disease, pulmonary metastases should be ruled out by roentgenogram of the lungs prior to attempting surgery.

Diffuse enlargement of the liver caused by von Gierke's disease, amyloid, or one of the malignant lymphomas may be confused

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*References 1-3 and 71.

with primary tumors. Lastly, a number of diseases involving other abdominal structures must be considered in differential diagnosis. These include the various types of abdominal cysts,[7] unattached retroperitoneal tumors,[8] hydronephrosis,[5] and tumors of the pelvic organs.[8]

PATHOLOGICAL-CLINICAL CORRELATION

The use of identical names for histologically different tumors of the liver has led to endless confusion. Most reviews have as a result been highly inaccurate. The terminology of liver tumors and the reasons for the choice of terms as used in this paper are discussed in another paper.[9]

When confronted with the problem of a liver tumor in an infant or a child, the clinician should be aware of those features that characterize specific tumors in this group.

In view of the clinical orientation of this discussion, specific tumor and tumor-like lesions will be emphasized and detailed in those instances where surgery may be undertaken with the view of effecting a cure.

BENIGN GROUP

1. Tumor-like Epithelial Lesions

Focal Nodular Hyperplasia.—Occasionally areas of circumscribed hyperplasia of liver cells form a firm multinodular, cirrhotic-appearing mass presenting beneath Glisson's capsule. The lesion may occasionally be pedunculated, or, on the contrary, located deeply within the liver. They are most often solitary, sharply demarcated, gray to gray-brown, and contain a stellate mass of connective tissue in their central portion (Figs. 1 and 2). As the connective tissue radiates toward the periphery of the lesion, it becomes less conspicuous. Histologically, these connective tissue strands contain many small bile ducts and lymphocytes, giving the lesion the appearance of cirrhosis. However, the architectural relationship between the connective tissue and the hyperplastic cells differs from that seen in other types of hyperplasia, especially the type following necrosis of the liver or that seen in Laennec's cirrhosis. In focal nodular hyperplasia, chiefly near the periphery of the lesion, spherical masses of hyperplastic liver cells are arranged around a central area of connective tissue, bile ducts, and blood vessels (Fig. 3). Even on biopsy these independent units are most helpful in diagnosis. The lesions also differ from other forms of hyper-

Fig. 1 (Courtesy of Dr. William M. Christopherson, Louisville).—Area of focal nodular hyperplasia 13×7×6½ cm. removed from left lobe of liver in a 12-year-old boy. Note the area of fibrosis in the central portion. (Permission to use this photograph, which was published in *Cancer* **6**:853-861, 1953, was given by Dr. Fred Stewart, editor of *Cancer*, and Dr. William C. Christopherson, Louisville, author of the article.

Fig. 2 (Christopherson and Collier,[10] Case 2).—Multiple pseudolobules of liver cells are arranged around a central mass of well-vascularized connective tissue in an area of focal nodular hyperplasia. Surgical specimen from a 7-year-old girl; reduced approximately ⅓ from mag. × 17.

plasia by their lighter color, which may well be related to their glycogen content. The latter in some instances is in a stable form similar to the glycogen stored in von Gierke's disease.

A variety of names, including adenoma, hepatoma, hamartoma, isolated solitary nodular hyperplasia, and focal cirrhosis, have been applied to this lesion. Although reluctant to add another synonym, I have chosen the term "focal nodular hyperplasia" until more is known of the disease.

There have been at least eight reported cases of this disease in infants and children.† There were four girls and four boys, ranging from 7 months to 14 years of age. The commonest symptom was that of an enlarging abdomen accompanied occasionally by localized pain. On physical examination the usual finding was a right upper quadrant mass that moved on respiration. In several instances, roentgenograms were helpful in their localization.

Surgery was undertaken in four of the eight cases. The pedunculated nodules were easily removable. When contiguous with the gall bladder, resection of the latter was necessary. In two cases, the areas of involvement were so large that surgical removal was impossible, and only a biopsy was done. These latter children have remained well.‡ In all, only one child died postoperatively.

In the surgical management of these cases, little diagnostic difficulty should be anticipated because of the characteristic gross and microscopic appearance of areas of focal nodular hyperplasia. Surgical resection should be done for the pedunculated forms and those easily resectable lesions near the margin of the liver. Large ones are better left undisturbed, as there is no evidence to suggest that they may become malignant or grow sufficiently to endanger life.

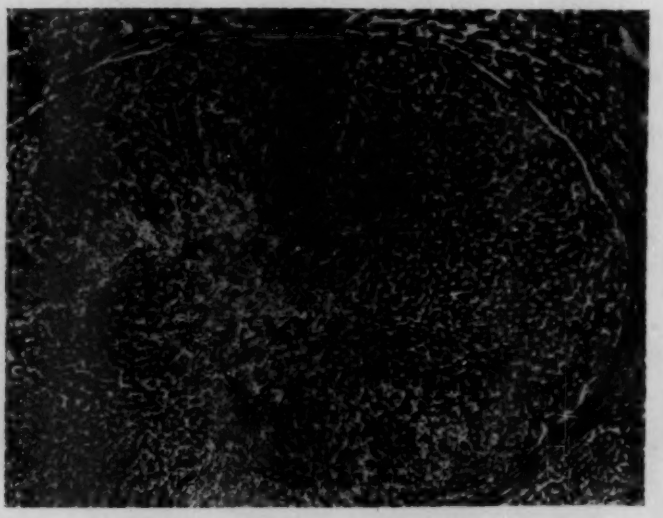


Fig. 3.—In this case of focal nodular hyperplasia the liver cells form a spherical mass about a central area containing bile ducts, blood vessels, and connective tissue. On the left is the line of demarcation between the hyperplastic cells and normal liver cells; × 75.

Multiple Nodular Hyperplasia. — Large palpable nodules may result from hyperplasia following acute necrosis of the liver. Some of these patients have been subjected to laparotomy for a supposed neoplasm of the liver. A careful history regarding antecedent liver disease along with the performance of liver-function tests should obviate such confusion in most cases.

Accessory Lobe.—An accessory lobe may occasionally be seen on roentgenograms, where it produces a localized elevation of a

† References 3, and 9-14.

‡ References 3 and 12, and personal communications from these authors.

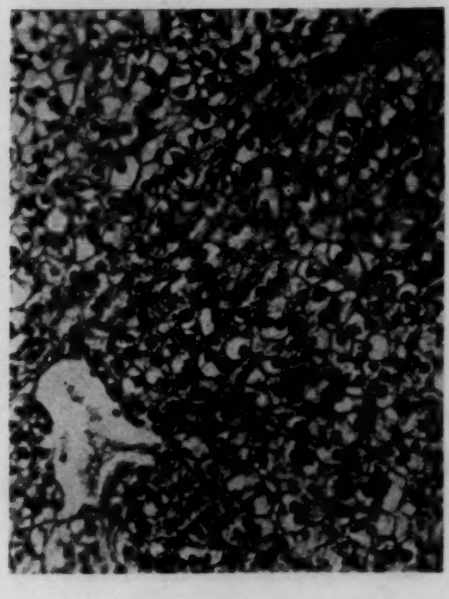
portion of the diaphragm.§ Recently we observed a huge tongue-like mass arising from the left lobe of the liver and partially filling the lesser peritoneal cavity in a 67-year-old woman. Normal hepatic tissue was found on biopsy. This was undoubtedly an accessory lobe present since birth. Accessory lobes are composed of normal liver tissue.

2. Benign Epithelial Tumors

Adenoma.—True liver-cell adenomas in infancy and children are extremely rare. Acceptable cases are those of Wilens [17] and of Christopherson and Collier (Case 3).[10] These tumors are encapsulated, gray-yellow to brown, and usually located in the right lobe. In Christopherson's case, that of a 13-month-old girl, the tumor was successfully resected. Histologically the hepatic cells in adenomas are similar to normal liver cells (Fig. 4). There are no bile ducts or portal tracts within the tumor. The diagnosis of adenoma of the liver should be made only after the evaluation of many histologic sections, including their comparison with known liver-cell carcinoma. Many of the cases diagnosed in children have subsequently been established as primary carcinoma, and in other instances they represent unquestioned cases of focal nodular hyperplasia. These inconsistencies make it impossible to arrive at conclusions relative to frequency and natural history of this tumor.

§ References 15 and 16.

Fig. 4 (Christopherson and Collier,[10] Case 3).—Liver-cell adenoma with vacuolated cells and distinct venous channels in a 13-month-old girl; reduced approximately ⅓ from mag. × 300.



The prognosis should be guarded because of the difficulty in distinguishing histologically identifiable adenoma from low-grade liver-cell carcinoma.

Adrenal Rest Tumor.—Heterotopic adrenal cortical tissue has been described beneath Glisson's capsule [19] on the inferior surface of the right lobe as early as the first month of life. Occasionally the entire gland may be so situated.[20] This ectopic tissue may, in rare instances, give rise to adrenal rest tumors in this location. A case reported by Wilkins and Ravitch [21] and one by Mason and Speese [18] are probably true adrenal rest tumors. In Wilkins and Ravitch's patient, symptoms of Cushing's syndrome were noted in a boy 2 years 10 months of age. The urinary 17-ketosteroids were increased. A palpable mass in the right upper quadrant of the abdomen was shown to be calcified on roentgenogram. At surgery the right adrenal could not be found and the tumor of the liver was resected. The symptoms of Cushing's syndrome disappeared, and the 17-ketosteroid level in the urine returned to normal. At 5 years 10 months of age the patient is still apparently normal. On histologic examination the tumor calls were similar to those of the adrenal cortex (Fig. 5). In Mason and Speese's case a malignant tumor of the liver in a 17-month-old boy was resected. It later recurred, accompanied by signs of adrenal cortical hyperfunction. This was probably an adrenal rest carcinoma of the liver.

The diagnosis of adrenal rest tumor must be approached with caution. It is probable that many of the tumors so diagnosed are in reality liver-cell carcinomas. At present it would seem best to make such a diagnosis only if there is evidence of adrenal cortical

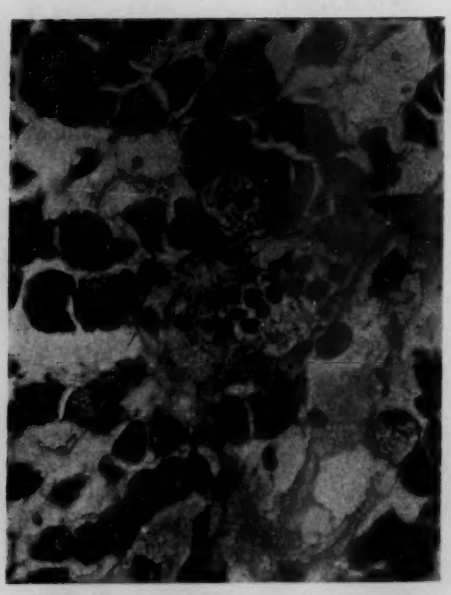


Fig. 5 (Courtesy of Dr. Lawson Wilkins, Baltimore).—Vacuolated adrenocortical type cells having a fascicular arrangement in relation to blood vessels; reduced approximately ⅓ from mag. × 550.

hyperfunction or when the hormones are identified in the tumor tissue.

3. Cysts and Tumor-like Mesenchymal Lesions

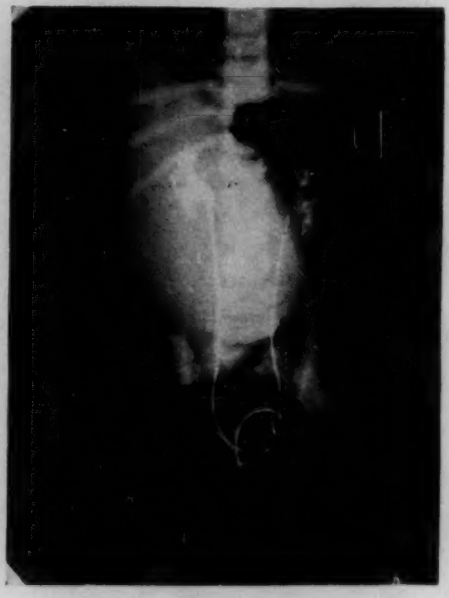
Mesenchymal Hamartoma.—A small group of cystic-appearing lesions that have been given a variety of names—cavernous lymphangiomatoid lesion; hamartoma; lymphangioma; solitary bile-cell fibroadenoma ‖—may properly be included under this designation. They are not true neoplasms and consist chiefly of connective tissue containing much serous fluid in association with a minor component of liver cells and bile ducts recognizable in and around remnants of portal triads. It seems justifiable to put into this group the reported cases of Lee,[22] Maresch,[23] Symmers and Ward-McQuaid,[26] Patton,[24] Potter,[25] Bartlett and Shellito,[21a] Packard and Palmer,[71] and four unreported cases—one from Craig at the Boston Children's Hospital, one from Foord at the Huntington Memorial Hospital of Pasadena, and two from the Los Angeles County Hospital.

‖ References 21a-26.

These hamartomas are probably congenital and usually become manifest prior to the age of 20 months. The patients present with a symptomless mass in the upper abdomen that may increase rapidly in size because of accumulation of fluid within the lesion. In every reported instance the hamartoma has been located near the lower margin of the liver and can frequently be outlined by x-ray (Fig. 6). They may have a broad pedicle and project downward into the pelvic cavity (Foord's case). The cystic appearance observed at surgery usually makes biopsy unnecessary for diagnosis. They are poorly demarcated from surrounding normal liver, as the connective tissue of the hamartoma merges with that of the portal triads. It probably is unnecessary to resect beyond the lesion into normal liver, as recurrence would appear to be highly improbable.

On superficial gross examination, the irregular cystic appearance of hamartomas is most characteristic (Fig. 7). On sectioning,

Fig. 6.—Roentgenogram of abdomen in a white girl of 20 months with a mesenchymal hamartoma. The outline of the mass in the right lobe of the liver extends into the pelvis and to the left of the midline.



the connective tissue is usually edematous and may be discolored due to old hemorrhages. Pseudocysts filled with pale, serous fluid are common, and the fluid escapes subsequent to cutting. On microscopic examination the most distinguishing feature is the large amount of collagenous connective tissue which is often quite mature and relatively acellular. In some of them, however, the connective tissue simulates primitive mesenchyme and contains angiomatous (Fig. 8) and hematopoietic foci. Some pseudocysts

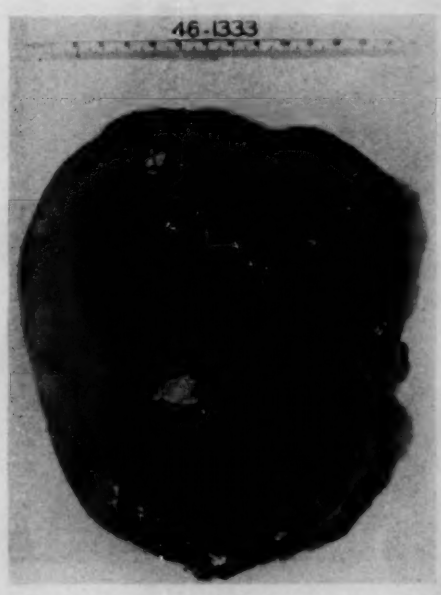
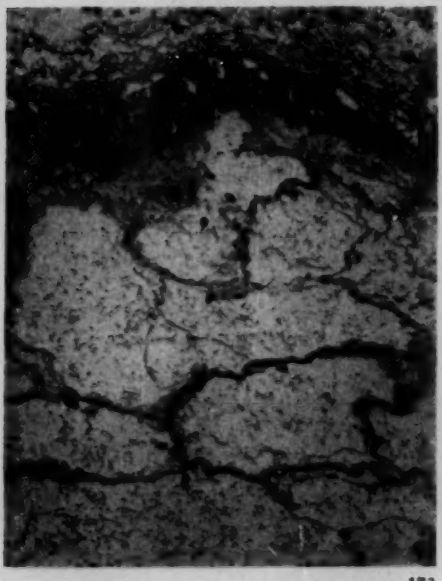


Fig. 7.—Mesenchymal hamartoma removed surgically from a baby boy of 12 months. Cyst-like structures filled with pale yellow fluid are conspicuous. Death occurred on the second postoperative day.

may have few or no lining cells; others may be lined with cells having the appearance of mesothelium. This suggests a possible origin from that portion of the celomic tract that gives rise to the mesenchyme of the liver anlage. Large dilated spaces filled with fluid (Fig. 9) have lead some observers to suggest that they are actually lymphangiomas. The absence of endothelial cells lining the spaces tends to negate this concept. A

Fig. 8 (Huntington Memorial Hospital, Pasadena, Calif., courtesy of Dr. Alvin G. Foord).—Dilated bile ducts surrounded by undifferentiated mesenchyme. Many cavernous angiomatous spaces at lower left. White girl of 8 months. Death was caused by size of tumor; reduced approximately ¼ from mag. × 85.

Fig. 9 (Children's Hospital, Boston, courtesy of Dr. Craig).—Characteristic cyst-like spaces with thin connective-tissue septa. Finely granular protein precipitate indicates they were filled with fluid; reduced approximately ⅙ from mag. × 120.



minor component of liver cells and bile ducts has been present in all cases (Fig. 10). These are most noticeable about the periphery of the lesion. Maturation of the connective tissue may produce distortion of the bile ducts, and some may undergo cystic dilatation. Liver cells may be present as solitary cords or in larger irregular groups. Occasionally, they may surround the portal tracts.

It is important that this group be distinguished from other tumor-like lesions and mesenchymal neoplasms and recognized as an entity that is amenable to surgery. The term hamartoma should not be applied both to this lesion and to focal nodular hyperplasia. There is no similarity in structure.

Nonparasitic Cysts.¶—Nonparasitic or solitary cysts occasionally occur in the liver. At the time of Munroe's [32] report in 1942 there were, including his own, 28 cases observed in children less than 13 years of age. Among patients of all age groups the frequency in females is four times that of males. These cysts are usually solitary. Occasionally multiple cysts occur localized to one portion of the liver. They are to be distinguished from polycystic disease in which there is an associated cystic involvement of the kidneys and, less commonly, the pancreas. Nonparasitic cysts may grow to great size in the infant. In some instances they have been so large that normal delivery of the fetus was prevented.#

Various complications, such as twisting of the pedicle, hemorrhage into the cyst, or suppuration, may produce acute symptoms. In one of Montgomery's [21] cases, the cyst wall was partially calcified and quite clearly outlined on x-ray examination.

At surgery they are seen most often at the anteroinferior margin of the right lobe of the liver. Occasionally they have been attached to the round ligament. They may be pedunculated and easily removed or they may lie deep within the substance of the right lobe and destroy most of it. The surfaces are smooth and gray to gray-blue and their fluid content is under low tension in contradistinction to the fluid in Echinococcus cysts. Dilated veins are usually present in the capsule. Those cysts that lie deep within the liver may be difficult or impossible to remove, and in such cases various means have been used to destroy the lining of the cyst. Marsupialization, anastomosis to the stomach, and dissection of the lining have all been successfully attempted in adults.* Recently a large nonparasitic cyst of the right lobe of the liver in a boy 2 years 9 months

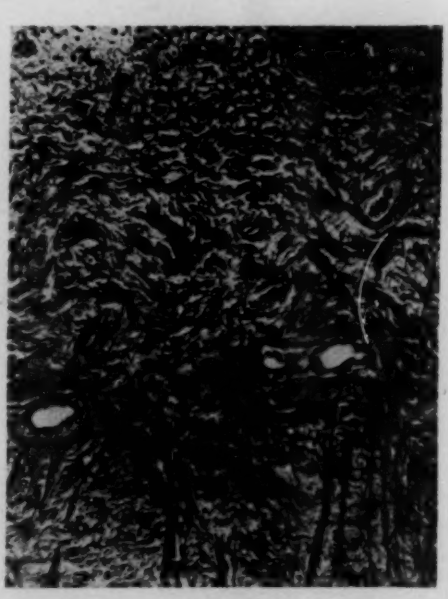


Fig. 10.—Same case as Figure 6. Small group of liver cells, mature connective tissue, and remnants of bile ducts; reduced approximately ¼ from mag. × 120.

old was successfully treated by partial resection and marsupialization at the Children's Hospital in Los Angeles.[34]

On histologic examination the epithelial lining of the cyst is similar to that of the bile ducts except for the occasional case where it is of the stratified squamous variety.[31] In large cysts the lining cells may be difficult to identify. The wall is composed of collagenous connective tissue, and often there

¶ References 28, 35, and 36.

References 27, 33, and 37.

* References 29 and 30.

is a thin layer of liver cells around the periphery.

4. Benign Mesenchymal Tumors

Cavernous Hemangioma.† — Pryles and Heggestad [45] recently reported the first successful resection of a cavernous hemangioma in an infant. The tumor, the sixth recorded case in the pediatric age group, occurred in an 18-month-old girl. Three of the five were in newborn infants who died from hemorrhage following rupture of the hemangioma.‡ The fifth case was that of a 6-year-old girl who died a month after resection of the hemangioma.[47] The remaining case is one mentioned by Ladd and Gross.[42]

The gross and microscopic appearance of cavernous hemangiomas of the liver is so well known that a description of them is unnecessary. It is of interest that in adults the clinical problem is seen predominantly among women who have had several pregnancies, suggesting that female sex hormones may be implicated in the growth of the tumor. In the six discussed cases two are girls and two are boys, and in the fifth and sixth cases the sex was not given.

Multiple or diffuse cavernous hemangiomas of the liver are extremely rare in infants.[43] These are distinguished from infantile hemangioendotheliomas by the fact that they do not form discrete nodules.

Infantile Hemangioendotheliomas.§ — Infantile hemangioendotheliomas are commoner than cavernous hemangiomas. They constitute one of the most interesting entities among all liver tumors. They occur in an age range from 36 hours to 4½ years. The clinical manifestations are commonest in the first weeks of life. An enlarged liver is ordinarily the first symptom, and when accompanied by hemangiomas of the skin the finding is almost diagnostic of the disease. Anemia may be present. Ascites and jaundice are rare. In some cases the symptoms are those of congenital heart disease. This has been attributed to arteriovenous shunts within the tumor.‖ Death usually occurs in less than six months.

Although the tumor has a benign histological appearance, death follows its progressive growth within the liver. This organ is usually filled with circumscribed nodular masses having a gray-white peripheral zone with a red to blue-purple center. The tumors average from 0.5 to 3 cm. in diameter and may be umbilicated. Rupture and intraperitoneal hemorrhage have been known to complicate the disease. Extrahepatic hemorrhagic nodules occur in about one-third of the cases, being seen most frequently in the skin, lymph nodes, and bones. These are not considered to be metastases, but independent multicentric growths.

Microscopically, hemangioendotheliomas are difficult to classify. They are composed principally of endothelial-lined channels of capillary size (Fig. 11). The vascular spaces in the center of the nodules are often cavernous, thus giving the characteristic red-purple appearance. Occasionally the endothelial cells may show moderate numbers of mitoses, and making a decision as to whether or not they are angiosarcomas becomes difficult. The tumors differ sufficiently from malignant vascular tumors in adults to require their consideration as a different disease.[8] Most authors regard them as malignant and fatal.

We have seen one example in a child 6 months of age who was operated upon in Children's Hospital in Los Angeles because of an enlarged abdomen. A liver filled with nodules was noted. A biopsy disclosed that the tumor consisted of vascular channels lined with endothelial cells three to four in depth (Fig. 12). It was interpreted as an angiosarcoma of the liver. However, five years later the child was apparently well and the liver was not palpable. This indicates that in some instances hemangioendotheliomas of the liver, even though multiple, may mature in a fashion similar to that of those

† References 38 and 44.

‡ References 39-41.

§ References 48, 50, and 51.

‖ References 49 and 52.

Fig. 11 (Courtesy of Dr. A. Sweed and Dr. T. Weinberg [50]).—Margin of an area of hemangioendothelioma of the liver. The tumors are composed of many capillaries lined with plump endothelial cells. They tend to grow with a solid front, as seen at the lower right, but occasionally they infiltrate along the sinusoids, as noted at the upper left; reduced approximately ⅓ from mag. × 220.

seen in the skin of infants.[1] Packard and Palmer [71] reported a similar case, in which a 3-month-old girl was noted to have a

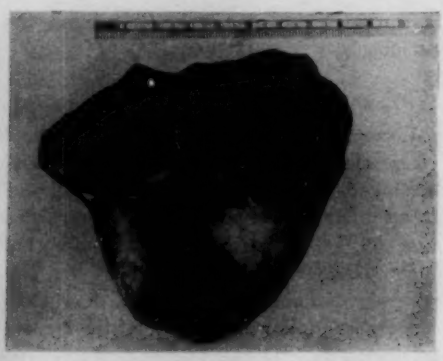


Fig. 13 (Courtesy of Dr. Lauren Ackerman).—This encapsulated solitary hemangioendothelioma, 6½ cm. in diameter, was removed from the left lobe of the liver of a 2½-month-old white boy.

markedly enlarged liver studded with nodular masses at surgery. A biopsy disclosed an "angiosarcoma." Four and a half years later the child appeared perfectly well and the liver was not palpable. This was in all probability another example of infantile hemangioendothelioma. Every effort should be made to keep these infants alive in the hope that the tumor may cease to grow.

One example of a solitary hemangioendothelioma (Fig. 13) that was successfully resected by the surgeon was contributed by Dr. Lauren Ackerman, of St. Louis. This tumor occurred in a 2½-month-old white

Fig. 12 (Children's Hospital, Los Angeles, courtesy of Dr. W. C. Thomas).— Hemangioendothelioma with both small and large vascular channels, thickened walls, and multiple layers of endothelial cells; × 285.

boy in whom a 5 cm. palpable mass was present in the left upper quadrant of the abdomen. A partial left hepatectomy was performed. No reports of similar cases were noted in the literature.

5. Teratoma

A few examples of true teratoma of the liver have been reported.¶ These are usually recognizable at birth or soon after. They are relatively benign and grow slowly. In one instance, a teratoma was successfully removed from a 7-week-old child.[55] This patient is now 12 years old and well. The term teratoid tumor of the liver should be discarded. A true teratoma is one in which there are tissues foreign to the liver, such as skin, brain, and respiratory tract derivatives. Because of these varied ailments, they have ordinarily a bizarre lobated structure on gross examination (Fig. 14).

6. Malignant Tumors

Primary Carcinoma.# — The commonest carcinoma of infancy is liver-cell carcinoma.[1] Boys under 2 years of age are most frequently affected. Only rarely do they complicate preexisting liver disease. In at least one case the tumor was congenital.[60] In those parts of of the world where there is a high frequency of liver carcinoma, there is a strange absence of reported cases of liver-cell carcinoma in childhood. The major symptom is gradual enlargement of the abdomen with development of a palpable mass. In contradistinction to most other tumors of the liver in childhood, there may be pain over the liver, anorexia, and loss of weight. Occasionally there are unusual manifestations of carcinoma of the liver in infants, such as hemihypertrophy and disturbances of the mineral and lipid metabolism.* The latter results in demineralization of the skeleton and an increase in all the lipid fractions of the blood. Presumably the demineralization of the skeleton is consequent to deficient calcium because of the lack of bile necessary for the action of vitamin D. Dr. Carroll Small, of Loma Linda, Calif., contributed a case in which the carcinoma of the liver was associated with extreme osteomalacia in a 9-year-old boy who was first seen by his physician at the age of 6½ years. At that time he had a shuffling gait. Roentgenograms disclosed cortical rarefaction of the skeleton. Nine months later the liver was noted to be 4 cm. below the costal margin, and on peritoneoscopy it was noted to contain nodules of variable size. At this time he became icteric and unable to walk. Death occurred two years five months after the onset of symptoms. At necropsy the liver was greatly enlarged and filled with green-brown nodular masses, one of which had ruptured through Glisson's capsule, causing fatal intraperitoneal hemorrhage. Postmortem x-rays disclosed an extreme degree of decalcification of the skeleton, with many old fractures and deformities (Fig. 15).

¶ References 53-55.

References 56 and 59.

Fig. 14.—Large, multilobed teratoma of the liver, weighing 1590 gm., surgically removed by Dr. Silas M. Yarbrough,[55] Gainesville, Texas.

Grossly, carcinomas of the liver in children form solitary or multinodular masses. They result in noticeable subcapsular tumors that are nonumbilicated (Fig. 16) or in multiple disseminated growths (Fig. 17). Usually they are fatty and often contain bile. As a result they appear yellow to yellow-green. As most tumors are liver-cell carcinomas, having only a capillary stroma, they are likely

* References 57 and 58.

Fig. 15 (Courtesy of Dr. Carroll S. Small, Loma Linda, Calif.).—Extreme osteomalacia of bones of lower extremities with pathologic fracture of the end of the femur, tibia, and fibula in a 9-year-old boy with liver-cell carcinoma.

Fig. 16 (Courtesy of Dr. Edward F. Ducey, Ventura, Calif.).—Multinodular liver-cell carcinoma appearing in a 11-month-old white boy. Note the nonumbilicated type of enlargement beneath Glisson's capsule. Multiple areas of hemorrhage are present throughout the tumor.

to be extremely soft to palpation when they bulge beneath Glisson's capsule, a significant fact for the surgeon. Some have sufficient stroma to form a firm mass. Those tumors that contain osteoid and areas of calcification may be visible on roentgenograms.

The microscopic appearances of liver-cell carcinoma vary considerably, but characteristically the cells are closely packed and smaller than those of liver-cell carcinoma in adults. Areas of fatty changes give the tumor a patchy pattern on scrutiny with low magnification (Fig. 18). Neoplastic, bile-filled canaliculi are common. Osteoid in small amounts (Fig. 19) is not infrequent and raises the question of their consideration as hepatic mixed tumors. Many carcinomas have such mature cell types (Fig. 20) that they have

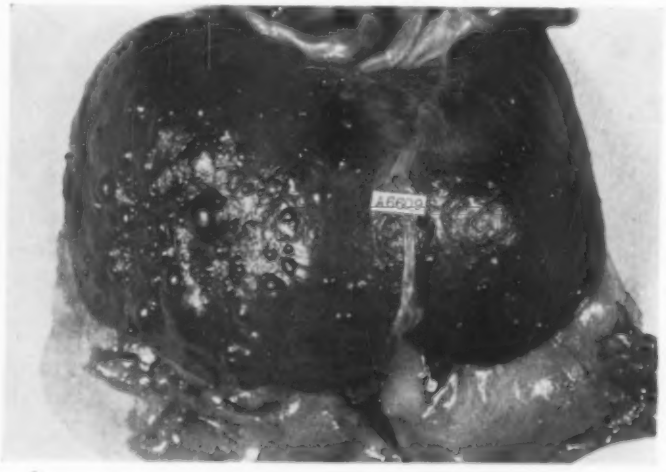


Fig. 17 (Babies Hospital, New York, courtesy of Dr. Dorothy Andersen).—Extensive multinodular type of liver-cell carcinoma, most prominent in the right lobe. The nodules are nonumbilicated, and some of them appear hemorrhagic. Infant 5 months of age.

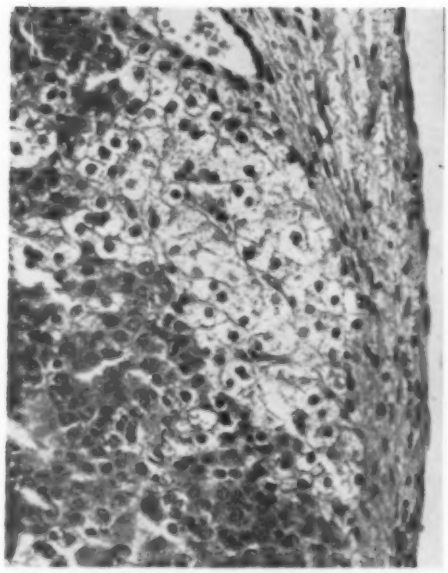
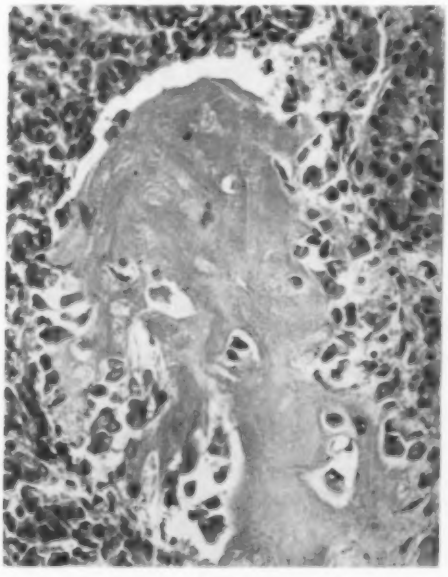


Fig. 18 (Cedars of Lebanon, Courtesy of Dr. Nathan B. Friedman).—Small, closely-packed cells in liver-cell carcinoma of a boy of 8 months. Note the patchy appearance caused by fatty change in the cancer cells; reduced approximately ⅓ from mag. ×240.

Fig. 19 (Children's Hospital, Los Angeles, courtesy of Dr. W. C. Thomas).—Area of osteoid in a liver-cell carcinoma. Many of the cancer cells are trapped within the osteoid; reduced approximately ⅓ from mag. × 220.



been consistently misdiagnosed as adenomas or benign hepatomas by pathologists. The literature is replete with such instances. This mistake can be avoided only by careful search for abnormal arrangement of the cords and sinusoids as well as for absence of normal lobular architecture in surgical material. At

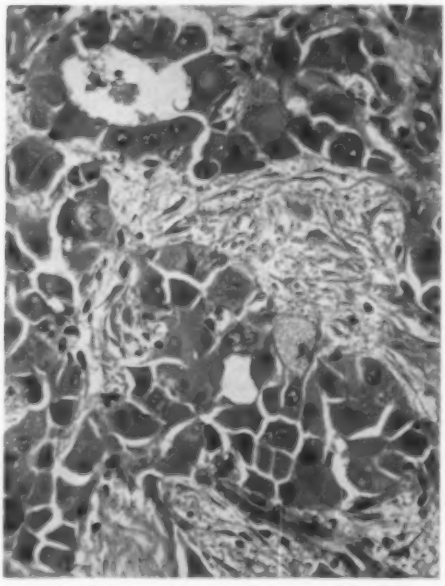


Fig. 20 (Pediatrics Tumor Registry, New York, courtesy of Dr. Alexander Brunschwig).—A liver-cell carcinoma of an adult type, in which the stroma is rather profuse and the similarity of the cancer cells to normal cells is striking. The tumor was resected in a 14-year-old white girl in May, 1952. There was no evidence of recurrence in June, 1954; reduced approximately ⅓ from mag. × 350.

all times one must remember how closely cancer cells may resemble normal liver cells.

The surgical treatment of liver-cell carcinoma has been disappointing, but with safer surgical techniques and more radical resection there is little reason why some of the well-differentiated tumors shouldn't be amenable to cure. Carcinomas often grow in a retrograde fashion in the intrahepatic branches of the portal vein, so particular attention should be given to this aspect during surgery.

Hepatic Mixed Tumors.—Hepatic mixed tumors are regarded as separate from tera-

tomas and mesenchymomas, but the exact limitations of this group are still debatable. Almost every gradation between liver-cell carcinoma with a small amount of osteoid stroma and the fully developed mixed tumor in which there is both liver-cell and bile-duct carcinoma intimately admixed with mesenchymal sarcoma may be seen (Fig. 21). Osteoid, cartilage, and even squamous-cell carcinoma are often present (Fig. 22). Those liver-cell carcinomas that contain only a minor component of osteoid may with considerable justification be omitted from the mixed-tumor group. Mixed tumors occur as a rule before the age of 8 years, with the majority seen in the first year of life. Girls are affected more frequently than boys.

Mixed tumors are usually solitary and involve the right lobe. They may be only a few centimeters in diameter or weigh up to 750 gm. Mixed tumors tend to grow rapidly and cause an increase in the size of the abdomen. In Milman and Grayzel's [62] case, however, there had been swelling of the abdomen for four and one-half years. In three reported cases the tumor was removed surgically.† It is of interest that although all of the tumors with a sufficient follow-up have been fatal, metastases are rare. The gross appearance at surgery differs little from that of liver-cell carcinoma. The diagnosis might be suspected if hard areas of bone or cartilage are palpable.

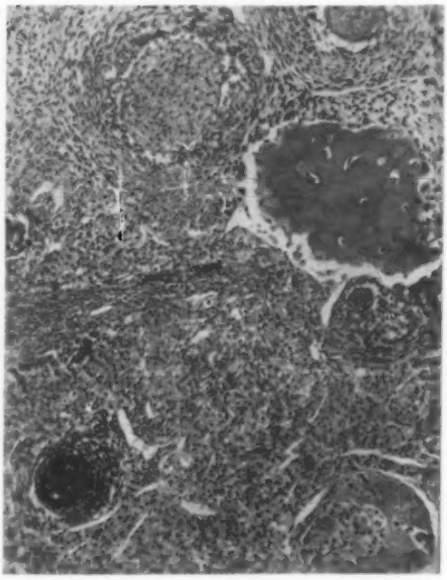
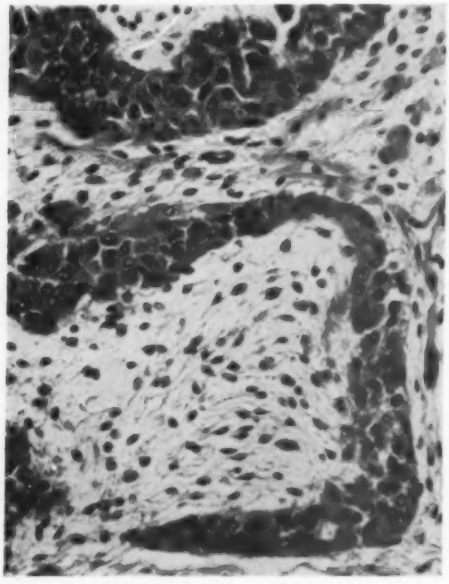


Fig. 22 (Courtesy of Dr. Robert Hebbel, Minneapolis).—Liver-cell carcinoma, osteoid, and area of squamous-cell carcinoma in the lower left; reduced approximately ⅓ from mag. × 75.

Fig. 21 (Courtesy of Dr. D. H. Milman and Dr. D. M. Grayzel, Jewish Hospital, New York).—Hepatic mixed tumor with the liver-cell component sharply outlined from mesenchymal sarcoma. A few intercellular fibrils have formed; reduced approximately ¼ from mag. × 320.



Hepatic mixed tumors are differentiated from other tumors of the liver containing more than one type of tissue by the intimate admixture of undifferentiated mesenchymal sarcoma with liver-cell carcinoma. They may both contain liver-cell carcinoma and bile-duct carcinoma. The examples the author has studied have all had varying amounts of osteoid.

Mesenchymoma. — Mesenchymomas include benign or malignant tumors that contain a variety of mesodermal derivatives.[63] Those seen in the liver have all been malignant.[1] The tumors are usually of considerable

† References 61-63.

size, firm, fleshy in appearance, and present beneath Glisson's capsule of either lobe. On histologic examination an undistinguished aggregation of fibrous, angiomatous, and undifferentiated mesenchymal cellular elements is usually seen. Osteoid and cartilage have thus far been undescribed. In some cases the presence of epithelial-lined cysts makes the differentiation of mesenchymoma from hepatic mixed tumors difficult. In two of three patients subjected to surgical removal of the tumor, there has been no recurrence.‡ In Lorimer's [64] case the time interval is still too short to be significant.

Sarcoma.—Sarcomas are rare. There is a marked scarcity of reported cases in the literature.§ In Andersen's [1] series of cases, however, they were more frequent than carcinoma. The author has had an opportunity to study some of Andersen's material. Most of them were spindle-cell sarcomas that were exceedingly difficult to classify. There was one rhabdomyosarcoma (Fig. 23) that was similar to the embryonal rhabdomyosarcomas described by Stobbe and Dargeon.[67] The others seemed to be composed for the most part of undifferentiated mesenchymal sarcoma. The treatment of choice is wide resection.

Secondary Tumors.—In the pediatric age group metastatic cancer of the liver is somewhat commoner than combined primary tumors and tumor-like lesions. Statistics as to frequency are lacking. In the material observed by Dr. Andersen at Columbia University, there were 24 secondary tumors of the liver and 20 primary tumors. Like primary tumor, metastatic tumors are also frequent before the age of 2 years. These are most likely to be secondary to a Wilms' tumor or a neuroblastoma of the adrenal gland. Clinically, metastatic neuroblastomas may be especially difficult to differentiate from primary tumors. As a rule metastatic tumors cause diffuse enlargement of the liver, the left lobe increasing in size concomitantly with the right, while primary tumors most frequently arise near the lower margin of the right lobe. Thus the shadow cast on roentgenogram and the physical findings may help in determining whether or not a palpable mass is confined to the right lobe or is caused by a diffuse enlargement of the liver. The same reasoning applies to von Gierke's disease.

Where metastases from a neuroblastoma are confined to the liver, excellent results from x-ray treatment have been reported.‖

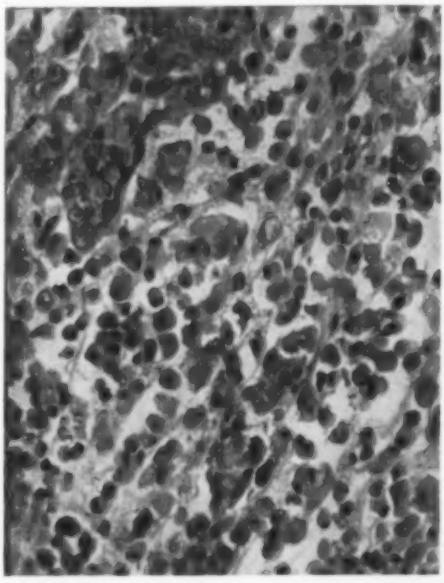


Fig. 23 (Babies Hospital, New York, courtesy of Dr. Dorothy Andersen).—Rhabdomyosarcoma of left lobe of liver in a white baby girl of 6½ months. The tumor was 11×10×6 cm. The tumor cells in this rhabdomyosarcoma are all uniform in size. The nucleus is often displaced toward one pole, the granular eosinophilic cytoplasm usually comprising most of the cell; reduced approximately ⅙ from mag. × 285.

In one case of metastatic neuroblastoma of the liver at the Los Angeles Children's Hospital, a child 5 months of age was treated by x-ray therapy in 1941. The last follow-up was in 1953, at which time he was living and well. In no other metastatic cancer of the liver can such favorable response to roentgen

‡ References 1 and 64.

§ References 1, 66, and 68.

‖ References 69 and 70.

therapy be expected. The finding of a large liver filled with metastatic cancer from a silent primary growth, a frequent clinical problem in adults, is not nearly so common in children. Among the first 40,000 necropsies at the Los Angeles County Hospital, there were three instances of metastatic cancer of the liver in children, but in only one was there any problem during life as to the location of the primary growth.

COMMENT

Many of the more important facts regarding the various tumors of the liver in infants and children are given in the Table. The features helpful in differential diagnosis are obvious. In the newborn period hemangioendotheliomas, solitary cysts, and cavernous hemangiomas are the most frequent. Between this period and 2 years of age, almost any of the benign or malignant lesions may be responsible for a palpable tumor in the liver. Beyond the age of two years, carcinoma, mesenchymoma and solitary cysts must be seriously considered. In three lesions predominance of one sex is noted; solitary cysts and hemangioendotheliomas are commoner in girls and carcinoma among boys.

In regard to symptoms, abdominal discomfort may accompany almost any of the large tumors, while actual pain is most likely to result from twisting of a pedunculated tumor or in association with malignant tumors. Rapid enlargement of the abdomen has been noted in mesenchymal hamartomas and in some of the malignant tumors. Although extremely rare, Cushing's syndrome may be caused by an adrenal rest tumor, and an increase in the 17-ketosteroids level in the urine may be demonstrable.

The skin should always be carefully inspected for hemangiomas in any child under one year of age that is suspected of having a liver tumor, as their presence is almost pathognomonic of hemangioendothelioma of the liver. Although no rules as to size can be followed, those tumors that are large enough to cause noticeable distention of the abdomen and cast a large shadow on roentgenogram are more likely to be solitary cysts, mesenchymal hamartoma, mixed tumor, or teratoma.

Certain of the neoplasms of the liver may show calcification on roentgenograms. These include liver-cell carcinomas, cavernous hemangiomas, adrenal rest tumors, mixed tumors, and occasionally solitary cysts.

At surgery the presence of a cystic tumor usually indicates a benign tumor, usually either a solitary cyst, a mesenchymal hamartoma, or a teratoma. Cysts may also be present in mesenchymomas and mixed tumors. Pedunculated lesions are also more likely to be benign. Focal nodular hyperplasia, solitary cysts, and mesenchymal hamartomas not infrequently have pedicles. Because of the benign nature of focal nodular hyperplasia, its distinguishing features should be kept in mind by the surgeon. They have a firm cirrhotic-like nodular appearance that lacks the areas of soft, friable tissue so characteristic of malignant epithelial tumors or the fleshy appearance of sarcomas. Areas of calcification, ossification, and cartilage if palpable would be indicative of a mixed tumor, carcinoma, or a teratoma.

When there is any doubt as to the diagnosis, a portion of the tumor should be removed for frozen section. This will allow the surgeon to perform a more radical operation should the tumor be malignant. Even though the prognosis is poor in this group, there is hope that in the future a higher percentage of patients can be salvaged by wider removal of the tumor.

The prognosis in the benign lesions is good. The major problem is concerned with improvement in surgical technique necessary for the removal of those tumors or cysts that may be situated deep in the right lobe. Recent reports indicate real progress is being made in this direction.

SUMMARY

A wide variety of tumors and tumor-like lesions occur in the liver of infants and children. They are commonest before the age of 2 years.

Symptoms are of little help in differential diagnosis in most instances. The exceptions

Tumor	Age	Sex	Symptoms and Findings	Laboratory	X-Ray Findings	Solitary or Multiple	Cystic	Calcification, Bone or Cartilage	Pedunculated	Prognosis
Focal nodular hyperplasia	7 mo.-14 yr.	F>M	Abdominal mass; pain not infrequent	.....	Nonspecific	Solitary	0	0	Often	Good
Multiple nodular hyperplasia	Any age	.....	History of acute hepatitis (?); palpable mass	Liver function tests may be abnormal	.....	Multiple	0	0	0	Depends on degree of liver damage
Accessory lobe	Any age	.....	None	.....	May cause localized elevation of diaphragm	Solitary	0	0	May have a broad pedicle	Excellent
Adenoma	8 [17] mo. 13 [10]	M F	Abdominal mass	.....	.....	Solitary	0	0	0	Presumably good, but may become malignant (?)
Adrenal rest tumor	2 yr. 10 mo.[21] 17 mo.[18]	M M	Cushing's syndrome	Increase in urinary 17-ketosteroids	R. lobe calcification may be present	Solitary in right lobe	0	May be calcified	0	Good if benign
Mesenchymal hamartoma	Less than 20 mo. in most cases	Equal	Abdominal mass, may grow rapidly	.....	Outlines of tumor often can be seen	Solitary near antero-inferior margin	X	0	Occasionally	Good if removed
Solitary nonparasitic cysts	Newborn-13 yr.	F 4-1 over M	Abdominal mass; pain if there is twisting of pedicle	.....	Capsule may be calcified	Solitary	X	Occasionally	Sometimes	Good
Cavernous hemangioma	Newborn-6 yr.	Equal	Palpable mass or shock due to rupture and hemorrhage	.....	Calcification may be present in older lesions	Solitary	0	0	0	Good if treated before rupture
Infantile hemangioendothelioma	Newborn-4 yr.; majority under 6 mo.	F 2-1	Nausea, vomiting, large liver, and hemangiomas of skin; occasionally symptoms of heart failure	Anemia frequent	Not characteristic	Multiple, umbilicated	0	0	0	Poor
Teratomas	Newborn-1 yr.	Equal	Abdominal mass	.....	Not characteristic	Large, multinodular	Often	Often	0	Good if removed
Primary carcinoma	Usually less than 2 yr.	M>F	Abdominal mass; occasionally pain, weight loss, pallor; ascites and icterus rare	Anemia	May show enlarged liver; occasionally calcifications or osteomalacia	Solitary or multinodular; nonumbilicated	0	Areas of calcification are rarely palpable	0	Poor
Hepatic mixed tumor	Usually less than 1 yr.	F>M	Rapidly enlarging abdomen	.....	Enlarged liver	Solitary; occasionally multinodular	0	Usually present	0	Uniformly fatal
Mesenchymoma	3, 6, and 15 yr. in 3 cases	.....	Enlargement of abdomen	.....	Not characteristic	Single nodular mass	May be cystic occasionally	0	0	To be determined
Sarcoma	?	?	Same as primary carcinoma	.....	.....	Usually solitary	0	0	0	Poor
Secondary tumors	Often after 2 yr.	.....	Frequently those of the primary neoplasm but first symptom may be enlarged liver	Anemia late	Large liver	Multiple umbilicated	0	0	0	Poor

are mentioned in the discussion of the specific tumors.

X-ray studies are helpful in localizing tumors of the liver. In order, these should include a flat plate and lateral roentgenogram of the abdomen, pyelograms, barium studies of the colon, and, lastly, barium studies of the upper gastrointestinal tract.

Roentgenograms may reveal calcifications in such tumors as liver-cell carcinoma, adrenal rest tumor, mixed tumors, and teratomas.

Criteria for the diagnosis of benign lesions are emphasized, as they are most amenable to surgical therapy.

Biopsy and frozen section are indicated when doubt exists as to the gross diagnosis. Histological criteria helpful in differential diagnosis of the more difficult lesions are given.

Resection of all primary malignant tumors of the liver should be undertaken if possible, as this offers the only hope of cure.

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News and Comment

ANNOUNCEMENTS

Eighth International Pediatric Congress: Arrangements for Visitors to London and U. K.—For those pediatricians who propose to pass through London on their way to Copenhagen for the Eighth International Pediatric Congress, The Hospital for Sick Children, Great Ormond St., is planning an "Open Day" on Thursday, July 19. In the morning parties will be conducted around the hospital and the Province of Natal Centre. In the afternoon there will be a series of clinical demonstrations. There will be exhibits in various departments of the hospital. The British Association of Paediatric Surgeons is arranging a meeting in London at the same time, and special programs are planned for surgical visitors. Visitors will be the guests of the Board of Governors to a buffet lunch and to tea, which will be available during the afternoon.

In order to facilitate personal arrangements for visits to other centers in London and elsewhere in the United Kingdom, an information bureau will be opened at the Institute of Child Health early in 1956. August and September are university vacation months, and in general it will be better for visits to be planned before rather than after the Copenhagen meeting. All requests for help in visiting other hospitals and university centers should be addressed to the Secretary, Institute of Child Health, The Hospital for Sick Children, Great Ormond St., London, W.C. 1. The bureau will deal only with personal plans, and all details regarding hotels, travel, and other arrangements must be settled through official agencies or by other means.

It will greatly help in the arrangements at The Hospital for Sick Children if intending visitors will notify the Secretary of the Institute of Child Health (see above) as soon as possible.

Abstracts from Current Literature

Newborn

PROLONGED JAUNDICE IN THE NEWBORN ASSOCIATED WITH CONGENITAL MYXEDEMA: A SYNDROME OF PRACTICAL IMPORTANCE. Y. AKERREN, Acta pædiat. **43**:411 (Sept.) 1954.

The author accounts for 10 cases of congenital myxedema with simultaneous icterus neonatorum prolongatus. From his series of cases and a critical analysis of the diagnostic criteria of icterus neonatorum prolongatus, the author draws the following conclusions: (1) The simultaneous occurrence of two comparatively rare conditions, such as congenital myxedema and icterus neonatorum prolongatus of prolonged duration, makes it highly probable that this is no chance coincidence. The further nature of the relationship between these two disorders is discussed. The general inhibition of the maturing of the functions of the organs and the reduction of the rate of the metabolic processes which distinguish the newly born with deficient thyroid function may explain why icterus neonatorum of unusually long duration can then occur. The possibility of an infectious origin, where both the thyroid gland and the liver are injured simultaneously, is also discussed. That this may occur is shown by a case published in France in which a virus infection simultaneously gives rise to lesions of the liver and of the thyroid gland with simultaneous jaundice and thyroid deficiency as sequelae. Such a pathogenesis was most probably not present in the cases described here. (2) The syndrome of congenital myxedema and icterus neonatorum prolongatus of marked duration is of practical significance in drawing attention to the possibility of a thyroid deficiency and thereby facilitating an early diagnosis of congenital myxedema. Icterus neonatorum prolongatus is, however, probably no constant phenomenon in congenital myxedema. (3) Icterus neonatorum prolongatus in the cases described here appears to have been of the physiological type of jaundice. However, the term physiological should not be employed unreservedly in icterus neonatorum prolongatus having a duration of six weeks or more.

FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

TREATMENT OF PERSISTENT DIPHTHERITIC INFECTION WITH ERYTHROMYCIN. J. A. FORBES, M. J. Australia **2**:501 (Sept. 25) 1954.

Fourteen patients harboring virulent diphtheria organisms were treated with erythromycin for a period of five days. Four days after cessation of treatment all virulent forms had disappeared, and no recurrence was noted.

McGUIGAN, Evanston, Ill.

TREATMENT OF LIFE-THREATENING POLIOMYELITIS. F. NEUKIRCH, Helvet. paediat. acta **9**:381 (Nov.) 1954.

On the basis of the results with regard to the large poliomyelitis epidemic of 1952-1953 in Copenhagen, the treatment of life-threatening poliomyelitis is described in detail. For the treatment of the pure respiratory-muscle paralysis, the tank respirator as well as the cuirass respirator have proved effective. However, as soon as difficulty with swallowing occurs, the patient is no longer in a position to maintain the airway free of secretions (wet form). Then the method of choice is positive-pressure breathing with the assistance of the Engstrom respirator. Thanks to the perfection of the techniques in handling the wet form of bulbar paralysis, the mortality of the bulbar form has been reduced in the course of a half year in Copenhagen from 87% to 11%.

FROM THE AUTHOR'S SUMMARY.

FIRST CASE IN SPAIN OF CONVULSIVE COUGH DUE TO PARAPERTUSSIS BACTERIOLOGICALLY PROVED. MANUEL MORENO LOPEZ and J. A. DE PAZ GARNELO, Acta pediát. españ. **11**:689-693 (Aug.) 1953.

The authors review the literature on the parapertussis organism and give the laboratory methods of distinguishing the three known organisms in the genus Bordetella. The clinical details

are given, and the authors state that the only difference between an infection due to Hemophilus pertussis and that due to parapertussis is the latter's greater resistance to medication.

ALLEN, Santa Fe, N. Mex.

MALNUTRITION AND IMMUNITY IN THE CHILD. FELIX SANCHO MARTINEZ, Acta pediát. españ. **12**:495-520 (June) 1954.

This is a review of the literature on malnutrition and its effects on the immunity of the children to various diseases.

In a large number of malnourished and an equal number of normal children complete studies of serum plasma protein were done. Electrophoresis methods were used, and the Hangar, Weltman, and McLagen reaction were obtained. The studies were done on the children at intervals beginning at 2 or 3 months and continuing until 3 years of age.

There was no definite tendency toward increase or decrease with age in the proteins or in the percent of albumin and β-globulins. There was a slight tendency in the decrease of α_1- and α_2-globulins as the age increased. There was a parallel increase in γ-globulins with increase in age.

Well-nourished children showed a slight increased protein as compared with malnourished children as age increased. Insignificant increases in α_1-, β-, and γ-globulins were shown in malnourished children as they grew older. Albumin figures were about the same in both groups of children.

The Hangar test was negative in all the normal children, but this was not true of the Weltman and McLagen test. Details regarding these tests and comments regarding reasons for possible variations are discussed. Complete protocols are included.

In 90 children of 3 to 11 years the following data regarding immunity were collected.

There was similarity in all nasopharynx organisms whether children were normal or poorly nourished. However, in three malnourished children a hemolytic Streptococcus was found which was not noted in the normal children, and one child in the malnourished group showed the presence of Pfeiffer's bacillus.

There was a greater opsonic index in the children suffering from malnutrition.

The titration of antibodies against diphtheria was the same in both types of children.

Positive agglutination of typhoid-paratyphoid was greater in number among malnourished but of greater intensity (higher titer) among the normal children.

Immediate cutaneous reaction to the injection of physiological salt solution was more rapid and more intense in normal children. The skin reaction remained longer in malnourished children.

The authors feel that except in extreme cases the immunity reactions between normal and malnourished children are not significant.

ALLEN, Santa Fe, N. Mex.

OBSERVATIONS ON AN OUTBREAK OF CHICKEN POX. C. SAINZ DE LOS TERREROS and J. A. DE PAZ GARMELO, Acta pediát. españ. **12**:550-533 (June) 1954.

The authors present two case histories and some remarks about the usually harmless disease of chicken pox. They discuss "cross infections" in children's institutions as the possible cause of deaths. The autopsy of the two children showed a purulent meningoencephalitis.

Although they found numerous cases of pneumonitis as a complication, no cases of lobar pneumonia or bronchopneumonia were found.

ALLEN, Santa Fe, N. Mex.

ELECTROCARDIOGRAPHIC CHANGES IN MEASLES. ELIAS BENGTSSON and ANDERS BERGLUND, Acta pædiat. **43**:426 (Sept.) 1954.

In a study of measles, 451 cases were examined electrocardiographically. Of these, 409 were children and 42 were adults; pathological electrocardiographic changes were found in 2 of the children (this is to say less than 0.5%) but in no less than 7 cases in the adults (16.7%). The changes were of a transient nature and lasted on an average two to three weeks, except in one case in which a right bundle-branch block arose in a 2-year-old child and was still present one year later.

FROM THE AUTHORS' SUMMARY.

A Study on Receptor-Destroying Enzyme in Saliva of Poliomyelitis Patients. B. Hofman, Maandschr. kindergeneesk. **22**:153-159 (May) 1954.

Receptor-destroying enzyme (R. D. E.) was first demonstrated in filtrates of cultures of Clostridium welchii and Vibrio cholerae. This enzyme prevents the agglutination of erythrocytes by influenza and other viruses. In the chicken embryo this enzyme can prevent infection. Erythrocytes incubated with R. D. E. become panagglutinable, the Thomsen-Friedenrich phenomenon. The enzyme is more frequently present and also in larger quantities in saliva of young children than in saliva of adults. The R. D. E. is found more frequently and in higher concentrations in patients suffering from poliomyelitis as compared with normal controls. The determination of R. D. E. has no diagnostic value in poliomyelitis.

van Creveld, Amsterdam.

Vaccinia Virus Cultured in Explanted Skin-Tissue of Bovine and Sheep Fetus. H. S. Frenkel and J. G. Kapsenberg, Nederl. tijdschr. geneesk. **98**:991 (April 10) 1954.

Frenkel and Kapsenberg prepared a vaccine against smallpox in vitro by means of a new, bacteriologically sterile method. As a tissue substrate they used fetal bovine and fetal sheep skin. From pregnant cows the intact uterus was removed and opened under aseptic care. The skin of the 20-40 cm. long fetus was removed by a sterile method. Mincing of the skin proved to be unnecessary. The effectiveness of the vaccine was first demonstrated in calves and rabbits. Thereafter 12 children under 2 years of age were inoculated simultaneously with the commonly used calves'-lymph virus and with both methods. It is not to be expected that postvaccinal encephalitis can be avoided by the use of the new vaccine. However, some components of the old vaccine are not present in the new, such as inflammatory products from the skin of the calf, degenerated leucocytes, and detritus of skin tissue. It may, however, be possible to gain a better insight in the problem of the postvaccinal encephalitis by use of the new vaccine.

van Creveld, Amsterdam.

A Syringe with Interchangeable Needle Suitable for Mass Vaccinations. R. Voorhorst, Nederl. tijdschr. geneesk. **98**:1984 (July 17) 1954.

The danger of viral hepatitis in mass vaccinations makes it necessary to use a fresh sterilized syringe each time. The Dutch industry constructed a new type of syringe which need not be sterilized each time. A special construction at the needle-syringe junction is made in which each time the needle is removed from this syringe there occurs no contamination of the syringe by aspiration of the contents of the needle. This syringe was used in a number of experiments with mice infected with pneumococci. These experiments proved the usefulness of the syringe for mass vaccinations.

van Creveld, Amsterdam.

A Case of Acute Hemorrhagic Edema. C. Postma and H. T. Deelman, Nederl. tijdschr. geneesk. **98**:2592 (Sept.) 1954.

A case of acute hemorrhagic edema in a 6-month-old girl with pertussis is described. The child recovered spontaneously. Histological examination of the skin mainly showed local arteritis in the media of the small arteries and proliferation of the intima of the precapillary arterioles. Acute hemorrhagic edema is probably allergic in origin.

van Creveld, Amsterdam.

Acute Infectious Diseases

Terminology of the Peracute Meningococcus Infections. H. K. Rechenberg, Schweiz. med. Wchnschr. **85**:502 (May 21) 1955.

The term "peracute meningococcus sepsis" designates a clinical picture of peracute rapid course with menigococci in the blood, with or without cutaneous hemorrhages, without changes in the spinal fluid, with severe collapse and signs of adrenal cortex insufficiency. "Meningitis epidemica maligna" means a peracute meningococcic infection similar to the peracute meningococcus sepsis but with apurulent meningitis. Both are grouped under the term "peracute meningococcus infection." "Waterhouse-Friderichsen-Syndrome" designates a pathologic-anatom-

ical condition characterized by cutaneous hemorrhages and bilateral massive hemorrhages in the adrenal cortex in the course of a severe acute illness. Hereby etiology and possible spinal fluid changes are irrelevant.

AMBERG, Rochester, Minn.

The DETERMINATION OF ISONIAZID IN THE URINE. J. F. M. HOELSCHER, Minerva pediat. **7**:157 (Feb. 10) 1955.

The author found on the basis of 35 observations that from 10% to 25% of isoniazid given orally or by intramuscular injection is excreted in the urine during the next 24 hours. The determinations were made using cyanobromide and spectrophotometry.

HIGGINS, Boston.

ANTIBIOTICS IN PEDIATRICS. CRESPO SANTILLANA, Acta pediat. españ. **12**:359-422 (April) 1954.

The author has written a very detailed discussion of the use of antibiotics alone and with other forms of treatment. Dosage details, those which are bacteriocidal and those bacteriostatic are included.

There is a chart which covers practically every disease likely to be found in pediatrics, with antibiotics listed in order of choice and comments on each in each particular disease.

ALLEN, Santa Fe, New Mex.

FEEDING OF PREMATURE INFANTS BY WAY OF PLASTIC CATHETER. J. L. CONCELLON MARTINEZ, Arch. pediat., Barcelona **5**:129-134 (Sept.-Oct.) 1954.

The author describes the use of a polyethylene catheter in premature infants, especially in those who weigh under 1500 gm. The advantage is that it may be left in for one to three weeks and the baby is not fatigued by the effort of sucking. If the catheter is fixed and the baby in the right position, aspiration is less likely to happen also. Serum, physiological electrolyte solution, and even oxygen may be introduced, as oxygen is absorbed by the gastric mucosa.

Other indications are for neonates suffering from dyspnea and anomalies of the mouth such as harelip and cleft palate.

ALLEN, Santa Fe, N. Mex.

STAPHYLOCOCCI INFECTIONS IN CHILDHOOD AND THEIR SIGNIFICANCE. W. MARGET and H. RICHARZ, Deutsche med. Wchnschr. **80**:725 (May 6) 1955.

The most important test to determine the pathogeninity of Staphylococcus aureus or Micrococcus pyogenes var. aureus is the coagulase reaction. Coagulase is very similar to prothrombin. Three phases of staphylococci infection are described, the first of which is represented by staphyloderma, as the primary phase. In the secondary phase foci are established elsewhere by way of hematogenous distribution. To this phase belongs for instance hematogenous osteomyelitis. In the tertiary phase a rapid transition to fulminant sepsis is imminent. The treatment of these phases and the indications for various antibiotics and for the use of an antitoxic Staphylococcus serum are discussed.

AMBERG, Rochester, Minn.

ALUMINUM POWDER IN OPEN-AIR TREATMENT OF WOUNDS. G. GRIESSER, Deutsche med. Wchnschr. **80**:1029 (July 8) 1955.

Aluminum powder in the form of "Medargal" was applied to burns immediately. Hot water and dry heat burns occurred in 65 children. Out of a total of 100 cases, the local treatment in conjunction with general treatment proved beneficial.

AMBERG, Rochester, Minn.

THE VALUE OF DISINFECTANTS IN DISEASE DUE TO DYSPEPSIA-COLI BACTERIA. G. FLEISCHHAUER, Med. Klin. **50**:740 (April) 1955.

A number of disinfectants was tried on colon bacilli $O_{111}B_4$ compared with Staphylococcus aureus. Various concentrations were used. Mercury bichloride and formaldehyde proved most efficacious. Ultraviolet light was tested in experiments with colon bacilli $O_{111}B_8$, $O_{26}B_6$, hemolytic streptococci, and staphylococci. With the lamp used most of the bacteria were killed at a distance of 1 m. in 20 min. Some strains required 60 min. exposure. With indirect application of the

ultraviolet rays, no inhibition was noted when the Petri dishes were placed on the floor or at height of the beds. As preventive measure, aside from isolation, mercury bichloride, 1:1000, was used exclusively for disinfection of hands and scouring. The bichloride was removed by water.

AMBERG, Rochester, Minn.

THE RELATION OF TONSILLECTOMY TO POLIOMYELITIS BULBAR PARALYSIS. W. LEUTERER, Med. Klin. **50**:886 (May 27) 1955.

The incidence of bulbar paralysis in cases of poliomyelitis is accepted as greater the shorter the interval between tonsillectomy and the disease. It is stated that the percentage of cases of bulbar paralysis is said to be relatively high in cases where this interval is considerable. The scar is regarded as a center of irritation, which reflects on the medulla oblongata, leading to assumed histochemical changes in the ganglion cells.

AMBERG, Rochester, Minn.

PROPHYLAXIS OF INTERSTITIAL PNEUMONIA OF PREMATURES WITH PLACENTAL BLOOD. K. DIETEL and V. DIETEL, Monatsschr. Kinderh. **103**:192-193 (March) 1955.

Based on the speculation that low γ-globulin levels of premature infants are related to lowered resistance and, therefore, to increased susceptibility to interstitial pneumonia, seven premature infants received intravenous placental blood prophylactically. It was given once to four infants and twice to three infants. All seven infants developed interstitial pneumonia. It was concluded that this method was unsuccessful in preventing interstitial pneumonia in premature infants.

HARTENSTEIN, Syracuse, N. Y.

ULCERATIVE ENTERITIS IN PREMATURE INFANTS. ULRICH KOETTGEN, EVA BRAUN, and GISELA WENGLER, Monatsschr. Kinderh. **103**:226-239 (April) 1955.

An outbreak of a highly contagious form of ulcerative enteritis in premature infants occurring in a hospital is described. Deaths were due to peritonitis or small-bowel perforation and occurred in several infants. Etiology was believed to be viral.

HARTENSTEIN, Syracuse, N. Y.

SUBACUTE BACTERIAL ENDOCARDITIS DUE TO LACTOBACILLI. H. J. DIETZSCH, Monatsschr. Kinderh. **103**:240-243 (April) 1955.

In a 9-year-old boy with ventricular septal defect who developed subacute bacterial endocarditis, lactobacilli were found on blood cultures during the initial episode and during a relapse. It was not possible to determine the exact type of Lactobacillus. One year following clinical cure the agglutination titer was 1:640, which was believed to be further proof of the bacteriological diagnosis.

HARTENSTEIN, Syracuse, N. Y.

Chronic Infectious Diseases

FATAL TOXIC ENCEPHALITIS OCCURRING DURING IPRONIAZID THERAPY IN PULMONARY TUBERCULOSIS. R. S. MITCHELL, Ann. Int. Med. **42**:417, 1955.

Iproniazid, the isopropyl derivative of isonicotinic acid hydrazine, is reported by the author to have caused a fatal toxic encephalitis in a 60-year-old patient suffering from tuberculosis. The drug was administered in daily doses of 4 to 5 mg. per kilogram of body weight, and approximately six months after treatment was initiated the patient complained of coarse tremors of both hands, tinnitus, mental confusion, and visual hallucinations. He gradually lapsed into coma and died.

Gross examination of the brain revealed numerous punctate hemorrhages in the cortex of the parietal and frontal lobes. Microscopic examination showed perivascular hemorrhages in the cortex and brain stem, as well as mononuclear infiltration in these areas.

The author believes that death may have occurred because of the acute nicotinamide deficiency which was induced by iproniazid therapy.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

OXYURIS VERMICULARIS: THE MOST PREVALENT PARASITE ENCOUNTERED IN THE PRACTICE OF PEDIATRICS. H. B. PRYOR, J. Pediat. **46**:262 (March) 1955.

If you want to be scientific about it you probably can find pinworm ova all over the house of your patient—on the fur of the cat or the dog, on the bedding, the night clothes, and the dust on the floor, and especially on the fingers and under the nails of the patient with an itchy bottom. Pryor stresses personal cleanliness in prevention. Antepar, with a cure record of 80%-85%, is a drug of choice.

MACDONALD, Pittsburgh.

THE TREATMENT OF PRIMARY TUBERCULOSIS IN INFANCY. M. MEYER, G. MIDDLEBROOK and A. ROBINSON, J. Pediat. **46**:398-402 (April) 1955.

To begin with, the authors suggest that routine tuberculin tests should be done on children during the first year of life, at the end of the second year, and every three years thereafter. Children exposed to tuberculosis should be given BCG. Infants with positive tuberculin and negative x-ray findings should receive a course of INH. Infants with positive tuberculin and positive x-ray findings should receive INH and streptomycin sulfate.

MACDONALD, Pittsburgh.

TUBERCULIN HYPERSENSITIVITY IN TUBERCULOUS INFANTS TREATED WITH ISONIAZID. ARTHUR ROBINSON, MARYETHEL MEYER and GARDNER MIDDLEBROOK, New England J. Med. **252**: 983 (June 9) 1955.

Sixteen infants with positive skin tests to 1:1000 OT. were treated with isoniazid for periods ranging from 5 to 17 months.

Four of these infants became negative to old tuberculin in 1:100 dilution. These babies had normal x-rays of the chest.

Two infants with normal chest x-rays remained sensitive to 1:100 old tuberculin.

The remaining seven babies all had abnormal chest films and remained positive to 1:1000 OT.

The conclusion is that decreased or reversion of tuberculin hypersensitivity is more likely in primary tuberculosis of a minimal type.

It is suggested that if such chemotherapy overcomes the infection to the extent that complete loss of hypersensitivity occurs, vaccination with BCG might be indicated. If reinfection should occur, a second course of chemotherapy could be started.

WHEELOCK, Washington, D. C.

LATE AND PROLONGED PRESENCE OF BACILLUS KOCH IN THE GASTRIC LAVAGE OF CHILDREN WITH PRIMARY TUBERCULOSIS INFECTION. A. BERTOYE, A. DEPIERRE and H. ROMIER, Pédiatrie **10**:259, 1955.

Systematic inocculation and culture of gastric washings in 44 children in whom at least one examination was positive have shown positive findings in 10 cases after one year and in one case after two years. The radiological findings in cases of prolonged bacillary emission are the same as those where bacilli could not be found. Glandulobronchial fistulas which might or might not be demonstrable by bronchoscopy, parenchymatous changes, bronchial stenosis or bronchiectasis, or minimal findings were associated with the positive gastric washings.

Medical treatment, consisting mainly of rest, is indicated, since healing occurs generally during the second year. Systematic administration of antibiotics is of questionable value. In one case the intrabronchial instillation of PAS has led to cure. Surgical treatment should not be considered before the end of the second year and after failure of medical treatment. The dangers of such persistent bacterial elimination to the patients are not well known, but they are certainly a source of contamination for others.

GLASER, Baltimore.

VACCINATION IN GREECE. SPIROS A. CAAROCOPOS, Indian J. Pediat. **21**:158-166 (July) 1954.

B. C. G. vaccine was administered to 25,000 children who were tuberculin negative. Of these, 85.8% became positive reactors after B. C. G. vaccination.

MCGUIGAN, Evanston, Ill.

PULMONARY SURGERY IN TUBERCULOUS CHILDREN. P. LOWYS and R. ROBINSON, Pédiatrie **10**: 283, 1955.

Twenty-five cases—3 segmentectomies, 14 lobectomies, and 8 pneumonectomies for various types of tuberculous lesions—are analyzed with regard to their immediate and later course, their indications, and pre- and postoperative management.

GLASER, Baltimore.

A New Concept of Immunization with BCG: The Brazilian Method. P. Lowys. Pédiatrie **10**:347, 1955.

Oral administration in large repeated doses without the need for previous skin testing and without isolation from contacts was originally advocated by Arlindo de Assis in Brazil. The author discusses the advantages of this method.

Glaser, Baltimore.

Allergy and Immunity in Infants Vaccinated with Massive Oral Doses of BCG According to De Assis' Technique. Evzen Kraus and Jindrich Dvorak, Presse méd. Supp. 81, p. 1680 (Dec. 4) 1954.

The authors studied in subjects vaccinated by BCG the simultaneous responses from a skin tuberculin test and an intradermal diluted BCG test; they consequently claim that the true immunity against tuberculous infection is expressed by the negativity and positivity to BCG as promptly (but not too markedly) observed.

The ideal in immunity would be a negative response to both tests. Absence of immunity is expressed by a positive tuberculin reaction together with a negative BCG test.

The authors have based their work on massive oral BCG vaccination according to De Assis' technique; they point out the innocuousness and preventive efficiency of this method, which have led them to preferring it to the dermal "unicalmetization."

From the Authors' Summary.

A Case of Tuberculosis of the Endomyocardium of the Heart. Virgilio Costa, Ann. ital. pediat. **7**:280 (Aug.) 1954.

The author describes a case of asymptomatic endomyocardial tuberculosis in a child of 2 years contemporaneously affected by miliary tuberculosis of lungs and tubercular meningitis. Primary complex was present in the right lung. The author discusses the pathogenesis of the endomyocardial tubercular damages.

From the Author's Summary.

The Diagnosis, Course, and Treatment of Infantile Kala-Azar. R. Ramos, W. Oppenheimer and J. Prats, Lattante **26**:1 (Jan.) 1955.

An analysis is given of 35 cases of kala-azar in children in a Barcellona hospital. Positive diagnosis was obtained by the demonstration of the parasites in the bone marrow smears in 34 of the cases; in the other case, no parasites were found in the bone marrow smear, but they were found in material obtained on splenic puncture. Blood cultures yielded positive results in 32 of the cases. If treatment with antimony preparations is started early, excellent results are obtained. In acute kala-azar, there is a marked increase in the amount of γ-globulin and a decrease in the albumin of the blood serum. The course and efficacy of the treatment is easily and efficaciously followed by frequent determinations of the γ-globulin:albumin ratio in the serum by paper electrophoresis.

When anemia occurs in kala-azar, it is usually due to destruction of the red cells by the enlarged spleen. Similarly, the platelet count is usually low in this disease.

Higgins, Boston.

Communication Regarding Modern Treatment of Osteoarticular Tuberculosis. Alvaro Lopez Fernandez, Acta pediat. espan. **12**:337-341 (April) 1954.

The director of the Sanitario Maritimo National in Valencia reports on the use of newer drugs in the treatment of osteoarticular tuberculosis. Statistics on 300 cases are cited.

Allen, Santa Fe, N. Mexico.

Tonsillectomy in Diphtheria Carriers. A. Montero Rodriguez, Acta pediat. españ. **12**:475-477 (May) 1954.

The author presents the brief case histories of children aged 5 and 6 years who had tonsillectomies for the indefinite reason of frequent upper respiratory infection and cervical adinitis. Four days following the operation both children developed diphtheria, typical in clinical appearance and proved by laboratory tests.

The author feels that throat smears and cultures before the operation should have been done and wonders if the operation did not cause greater susceptibility just as it does in acute anterior poliomyelitis.

Penicillin and antidiphtheria serum gave prompt relief and recovery.

ALLEN, Santa Fe, N. Mexico.

Diseases of Blood, Heart and Blood Vessels, and Spleen

RHEUMATIC HEART DISEASE IN SCARLET-FEVER PATIENTS WITH PENICILLIN. LOUIS WEINSTEIN, NORMAN H. BOYER, and MARTIN GOLDFIELD, New England J. Med. **253**:1 (July 7) 1955.

A group of 110 patients with scarlet fever treated with penicillin in 1946, of whom 100 showed normal electrocardiograms and 10 prolongation of conduction after a latent period, were restudied in 1953. None of those without electrocardiographic changes in 1946 had any evidence of cardiac disease in 1953. Of those with prolonged P-R and Q-T intervals seven years earlier, eight (7.9%) had definite or "probable" rheumatic heart disease. In six (5.9%), mitral insufficiency and stenosis were present; two of these had aortic as well as mitral lesions.

The data presented suggest that penicillin therapy of streptococcal pharyngitis in children, even when applied early, may not significantly decrease the occurrence of acute rheumatic carditis.

In children the clinical features of the acute rheumatic state may be markedly suppressed by the chemotherapy of the initiating streptococcal infection, so that most or all of the characteristic signs and symptoms are absent, and electrocardiographic evidence of carditis becomes the most prominent and sometimes the only diagnostic feature. Because of this it is probably necessary to redefine the present criteria for the diagnosis of acute rheumatic fever, particularly for children with antibiotic-treated streptococcal pharyngitis.

Demonstration of prolonged atrioventricular conduction time, after a latent period, probably is highly significant for the diagnosis of rheumatic carditis in the absence of "major" manifestations if the patient can be proved to have had a recent streptococcal infection.

FROM THE AUTHORS' SUMMARY.

CHOREA AND RHEUMATIC FEVER IN INFANCY. JOSE SELFA, Acta pediat. españ. **12**:341-352 (April) 1954.

The author discusses some of the changing ideas regarding the association of chorea with rheumatic fever. Chorea lacks anatomical characteristics, such as Aschoff nodules, and clinical signs, such as fever and elevated sedimentation rate. Perhaps chorea is associated with infections but not solely limited to the infectious process of rheumatic fever. In the 136 cases studied, one case came to autopsy, and an inflammatory process and edema were found in the hypothalamic region. The possibility of a neurotropic virus as causal agent is discussed.

It is possible that chorea like rheumatic fever is a disease of adaptation due to excessive secretion of the mineral cortocoids.

Statistics regarding the percentages with throat infections, cardiac changes, and articular changes are given in the form of a graph.

Several cases were precipitated by a psychic trauma.

ALLEN, Santa Fe, N. Mex.

A FAMILIAL HEMOLYTIC ANEMIA FOUND IN THE PHILIPPINE ISLANDS. EUGENE STRANSKY and AMBROSIO REYES, Acta pediat. españ. **12**:425-438 (May) 1954.

Three cases of the type of chronic hemolytic anemia first described by Stransky and Regala are reported in this study. The first case had been under observation since infancy until the present—a period of 14 years. Although the authors have examined and studied about 60 cases, these 3 are presented in detail. They are not like Mediterranean anemia, and the details of the differences in blood picture are described.

In contrast to thallassemia, the hypochromic anemia is never marked; there are frequent hemolytic attacks which are not improved by splenectomy. The Philippine type of anemia may begin at any age. There is always severe anemia and icterus, yet despite this the disease is compatible with life. The Mediterranean disease is definitely recessive as to genetics, whereas the disease here described is probably a dominant germ-plasm defect.

ALLEN, Santa Fe, N. Mex.

SIDE-EFFECTS OF SOLUBLE PYRAZOL COMPOUNDS ON TREATMENT OF RHEUMATIC FEVER. W. FALK and E. SEKOL, Wien. klin. Wchnschr. **67**:393-397 (June 3) 1955.

Seven children with acute polyarthritis or endocarditis rheumatica were treated with Irgapyrin (aminopyrine dissolved with the aid of Butazolidin), given intramuscularly. In four patients hematuria occurred, in three, hemorrhages into the skin and mucous membranes. Only one patient showed a severe disorder of the general condition together with an abnormally low thrombocyte count (84,000).

In experiments on rats, the effect of Irgapyrin, Butazolidin, and Aminopyrine was studied determining the number of erythrocytes, thrombocytes, and leucocytes. There was little effect on erythrocytes and leucocytes, but thrombocytopenia was noted in the peripheral blood.

AMBERG, Rochester, Minn.

ATYPICAL RETICULOSES. P. DENYS and H. MALBRAIN, Acta pædiat. belg. **8**:313, 1954.

A case of an atypical reticuloendotheliosis in a child of 22 months is discussed and a classification attempted.

GLASER, Baltimore.

DIFFUSE EOSINOPHILIC GRANULOMA. J. RICHARD and R. DELCOURT, Acta pædiat. belg. **8**:320, 1954.

A case of a diffuse eosinophilic granuloma of the bones, whose very rich symptomatology suggested Hand-Schüller-Christian's disease, is described. Two years later the child appeared cured, showing as sequelae diabetes insipidus and bone deformities.

GLASER, Baltimore.

Diseases of Nose, Throat, and Ear

A STUDY OF LYMPHOID TISSUE OF THE NASOPHARYNX. PHILIP E. MELTZER, Ann. Otol. Rhin. & Laryng. **63**:607 (Sept.) 1954.

According to Meltzer, the problem of nasopharyngeal lymphoid tissue resolves itself into two categories: the rhinological and the otological. When nasopharyngeal lymphoid tissue obstructs the nasal airway, subsequent removal usually satisfactorily solves the problem. When the nasopharyngeal mass encroaches on the Eustachian tube simply by contiguity, any interference with tubal function can similarly be corrected by surgical removal of the mass. However, when tubal dysfunction recurs after operation, either following or in the absence of upper respiratory infection, then it is apparent that there must be residual lymphoid tissue either in the fossae of Rosenmüller, within the tubal orifice, on the torus, the salpingopharyngeal bands, or salpingopalatine bands.

Irradiation acts on the secondary nodules of nasopharyngeal lymphoid tissue and manifests itself in three stages: first, cessation of proliferative activity; second, conspicuous scavenger activity, during which the destroyed cells are removed; third, depending on the dosage used, the return of proliferative power. Irradiation by any means—x-ray, radium, or ultraviolet rays—produces the same effect. The author prefers x-ray irradiation.

Surgery has the advantage over irradiation in that it actually removes the mass of lymphoid tissue. Lymphoid regrowth which results in tubal closure is best managed by considering the patient's history and the findings by direct vision at the time of operation. If loss of hearing has followed tubal closure after upper respiratory infections but has returned to normal after a few inflations of the tube, the obstructing lymphoid tissue is removed surgically. If, on the other hand, the tubal occlusion recurs after an upper respiratory infection and inspection of the nasopharyngeal vault shows it to be free of nodules, irradiation is advised. Six hundred roentgens in three treatments (100 r to each side through an intraoral cone or over the lateral neck) is the dose used.

If the patient has recurring tubal closure without upper respiratory infection and lymphoid tissue is noted, the lymphoid tissue is thoroughly removed by surgery and x-ray treatments are started two weeks following surgery. If this fails to produce desired results, allergic studies are started, whether or not the patient shows clinical evidence of allergy.

Where the patient is known to have a history of allergy but has failed to respond to allergic management, the nasopharyngeal lymphoid tissue is removed surgically. If there has been no

allergic treatment and the patient shows clinical signs of allergy, then allergic management is instituted first. If there is poor response, surgery is performed. Whether or not irradiation is then given depends on the postoperative course.

STEELE, Kansas City, Kan. [A. M. A. ARCH. OTOLARYNG.].

Diseases of Lungs, Pleura, and Mediastinum

HYPOPLASIA OF THE LUNG ASSOCIATED WITH CONGENITAL DIAPHRAGMATIC HERNIA. RALPH P. CAMPANALE and ROBERT H. ROWLAND, Ann. Surg. **142**:176-189 (Aug.) 1955.

Congenital diaphragmatic hernias are reported with such frequency that they can no longer be classed as pathological curiosities. The most frequent type occurs through the pleuroperitoneal canal. Left-sided lesions are approximately 12 times commoner than these on the right side. The association of hypoplasia of the lung with congenital hernia of the diaphragm is rarely encountered in the surgical literature, although it is not an uncommon finding in the pathologic laboratory. Newborn infants with this combination of defects rarely survive the immediate postnatal period.

The authors report in detail five cases of hypoplasia of the lung associated with congenital pleuroperitoneal hernia. Two died before operation could be done and three shortly after operation. They feel that prognosis is poor but not hopeless.

BANTIN, Omaha.

ESSENTIAL PULMONARY HAEMOSIDEROSIS AS AN IMMUNO-HAEMATOLOGICAL PROBLEM. BELA STEINER, Arch. Dis. Childhood **29**:391 (Oct.) 1954.

A case of essential pulmonary hemosiderosis diagnosed during life is described. Diagnosis was made by thoracotomy.

As a therapeutic measure splenectomy was performed. Thereafter the disease ceased to progress, and not a single attack associated with anemia was observed for 12 months. This is the fourth case in the world literature improved in this way.

Essential pulmonary hemosiderosis is considered to be an immunoallergic disease, caused by a still unknown sensitizing agent inducing the production of autoantibodies. The antigen-antibody reaction causes in the lungs, as the shock organ, capillary dilatation, consequent stasis, diapedesis, rhexis, increased destruction of the injured red corpuscles, and deposits of hemosiderin.

Early diagnosis must be aimed at, since in this way there is hope for complete restoration to health.

KELLY, Milwaukee.

CONGENITAL PNEUMONIA AND PNEUMONIA IN THE NEONATAL PERIOD. K. HARNAES and K. H. TORP, Arch. Dis. Childhood **30**:99 (April) 1955.

In postmortem material comprising 169 stillborn infants and 253 infants who died in the neonatal period, pneumonia was observed in 84 infants, 60 of whom were stillborn or died within the three first days.

These 60 cases have been distributed into two main groups: (1) infants infected before or during delivery; most of these were large infants, and the mothers were, as a rule, elderly primiparae; (2) infants probably infected after delivery by airborne infection; half of these were premature. Massive pneumonia was seen in premature infants dying during the first day, even after entirely normal births.

The prophylactic treatment of mother and child should be planned to combat both these two modes of infection.

KELLY, Milwaukee.

BULLOUS OUTLINES APPEARING IN A CHEST X-RAY OF A PREMATURE INFANT. M. BELLONI, Lattante **26**:171 (March) 1955.

An x-ray film taken of the chest of a 21-day-old premature infant revealed two large bullous outlines; they had disappeared by the time the infant was 2 months old. The diagnosis seems to be an emphysematous bleb; their appearance is not uncommon in premature infants.

HIGGINS, Boston.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

DIARRHEA IN INFANCY; ETIOLOGY AND TREATMENT. J. N. ETTELDORE, J. Louisiana M. Soc. **106**:334-341 (Sept.) 1954.

Diarrhea has been classified by etiology and treatment outlined in some detail. By using these methods, the reduction of the mortality rate to 3% among hospitalized patients was achieved.

McGUIGAN, Evanston, Ill.

DUODENAL OBSTRUCTION DUE TO ANNULAR PANCREAS WITH THE DIFFERENTIAL DIAGNOSIS OF OTHER CONGENITAL LESIONS PRODUCING DUODENAL OBSTRUCTIONS. JOHN W. HOPE and JOHN F. GIBBONS, Radiology **63**:473-509 (Oct.) 1954.

Eight cases are presented with a varying degree of pancreatic tissue passing more or less around the second portion of the duodenum. Loose fibrous tissue on the ventral surface may complete the circle. High-grade stenosis usually occurs. While the x-ray appearance simulates that of fibrous bands, the constricted zone is not as narrow, and this is considered an important sign by the authors. Small air bubbles may be seen beyond the zone of obstruction and aids in differentiating this condition from complete atresia. Webs or membranes across the lumen of the diaphragm and paraduodenal hernia are rare lesions that have to be considered.

The authors recommend the withdrawal of fluid from the stomach and dilated duodenal bulb and injection of 50 cc. of air; they emphasize the value of erect, both decubitus, and sometimes upside-down roentgenograms.

The treatment consists of a surgically by-passing procedure rather than simple section of the anterior ring.

ANSPACH, Riverside, Ill.

BLEEDING LESIONS OF THE GASTROINTESTINAL TRACT IN INFANTS AND CHILDREN. JOHN R. HODGSON and ROGER L. J. KENNEDY, Radiology **63**:535-541, 1954.

The differences in etiology of hemorrhage among 246 children of various ages are listed and and discussed. Under 2 years of age intussusception was the commonest, while between 2 and 6 years of age polyps of the colon occurred oftenest, and between 7 and 15 chronic ulcerative colitis was most frequently encountered. The commonest causes of bleeding in the entire group occurred in the following order: chronic ulcerative colitis, polyps of the colon, Meckel's diverticulum, and intussusception. The source of bleeding was not determined in 19 cases.

ANSPACH, Riverside, Ill.

DUODENAL INTUBATION UNDER FLUOROSCOPIC SCREEN CONTROL. C. H. Ward, G. N. WEBER, and J. M. WELLS, Great Ormond St. J. (No. 7) pp. 73-76 (June) 1954.

The technique of duodenal intubation using fluoroscopic observation is outlined. The author points out that, as in threading a needle, it is easy to do if you can see when you have missed.

McGUIGAN, Evanston, Ill.

Nervous Diseases

AQUEDUCT STENOSIS: CLINICAL ASPECTS AND RESULTS OF TREATMENT BY VENTRICULOCISTERNOSTOMY (TORKILDSEN'S OPERATION). KENNETH W. E. PAINE and WYLIE McKISSOCK, J. Neurosurg. **12**:127, 1955.

Occlusion of the aqueduct of Sylvius may be caused by congenital malformation, post-inflammatory ependymitis, neoplasms, or aneurysms. One method of overcoming this obstruction was devised by Torkildsen, who provided a new Sylvian aqueduct by passing a soft rubber tube from one lateral ventricle through a sublgaleal tunnel over the occiput and into the lower end of the cisterna magna.

Paine and McKissock report their observations in a series of 24 cases treated by the Torkildsen method for non-neoplastic aqueduct obstruction. Symptoms developed before the age of 20 years in approximately two-thirds of the patients, the shortest duration of complaints being 3 weeks and the longest 46 years. Headache was the commonest symptom. It was bifrontal or bitemporal, was worse in the morning, was aggravated by exertion, and cleared during the day.

It was frequently accompanied by nausea and vomiting. Visual impairment and mental changes were noted in 11 cases, unsteadiness of gait, double vision, and seizures comprising the remainder of the symptoms. The objective findings included evidence of papilledema, in 21 cases, diminished visual acuity, nystagmus, increased head size, and pyramidal tract signs. Roentgenograms of the skull demonstrated raised intracranial pressure in 20 cases, with erosion of the dorsum sellae and digital markings of the vault. Large diploic channels were noted in the occipital bone over the posterior fossa. With benign obstructions in childhood, there was a greater relative enlargement of the supratentorial portion of the skull than when the obstruction was in or below the fourth ventricle, where the posterior fossa would be enlarged by the tumor and the supratentorial portion would be enlarged by hydrocephalus. The authors performed ventriculograms with iophendylate (Myodil; Pantopaque) in 12 cases in order better to visualize the obstruction of the aqueduct. With this method the obstructed aqueduct appeared to be occluded, had a bulbous or funneled shape, or was noted to be atresic.

The short-circuit operation was successful in 18 cases (73%), although successful economic results were obtained in only 9 out of 21 followed for more than a year. There were five postoperative deaths in the series. The authors conclude that hydrocephalus caused by aqueduct stenosis can be relieved by this shunt operation, but visual deterioration is unlikely to be reversed by the procedure. With earlier diagnosis, the late results of this procedure may be improved, as the shunt operation is successful in most cases.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

OBSERVATIONS ON VENTRICULAR AND LUMBAR SUBARACHNOID PERITONEAL SHUNTS IN HYDROCEPHALUS IN INFANTS. MICHAEL SCOTT, HENRY WYCIS, FREDERICK MURTAUGH and VICTOR REYES, J. Neurosurg. **12**:165, 1955.

The authors report their results with ventriculoperitoneal and lumboperitoneal shunts in the treatment of progressive hydrocephalus in 32 infants. They noted that the operative procedure was well tolerated in all cases and the operative mortality was 5%. Surgical results were better in the 22 cases of communicating hydrocephalus than in the noncommunicating type. In this series a stainless steel button was suspended into the peritoneal cavity and the extraperitoneal portion connected to a rubber tube which was placed in the ventricle or subarachnoid space. It was found that the rubber tubing was superior to plastic tubing, since the latter has the disadvantage of kinking when bent and becomes brittle when in contact with the spinal fluid over a long period of time. The rubber tube was well tolerated in the ventricles, and only a slight capsular reaction was noted in the subcutaneous tissues of the skin. The stainless steel button was satisfactory in only 50% of the cases, being frequently obstructed by omentum. The authors conclude that the shunt operations should not be abandoned, since the operative mortality is low and lives may be prolonged.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Diseases of Genitourinary Tract

PROBLEMS OF ELECTROLYTE AND WATER BALANCE IN NEPHROTIC SYNDROME. JOHN A. LUETSCHER JR., A. M. A. Arch. Int. Med. **95**:380 (March) 1955.

This article is one of five which compose a symposium on electrolyte and water balance. The author reviews the subject of electrolyte imbalance in patients with the nephrotic syndrome and points out that many will show abnormalities of serum sodium and potassium concentration which are related to the disease and to the therapeutic measures aimed at control of edema. He outlines in detail the therapeutic measures to be used when such a situation occurs and gives one case history.

JONES, Chicago.

DIAGNOSIS AND TREATMENT OF MALIGNANT TUMORS OF THE KIDNEY IN CHILDREN. RENE HUGENIN and REMI GERARD-MARCHANT, Presse méd., Suppl. 44, p. 909 (June 24) 1953.

Among all cancers affecting children, incidence of malignant tumor of the kidney before 15 years of age is notable (about a third of the total). From 1933 to 1951, sixty-four cases of malignant tumor of the kidney were observed in children at the Cancer Institute Gustave-Roussy. They were histologically identified by examination of the specimens from operation or necropsy.

The authors' purpose is not to insist upon the theoretical aspect of these tumors but to provide the physician with some pathologic data, the knowledge of which is essential for the

conduct of treatment. Two fundamentals do prevail, fragility of the tumors and their propensity to metastases. Any maneuver risking to "traumatize" the tumor as well in diagnostic as therapeutic stage should be avoided since prognosis is very poor as soon as metastasis is present. Radiographic, pyelographic investigations are described.

Roentgentherapy with usual voltage (200-300 kv.) proved more effective than telecurietherapy. The treatment is detailed. Stress is laid on the importance of not missing symptoms and signs suggestive of renal tumor, as was often observed. Some cases are reported as illustrating this fact. Indications for the surgical operation are discussed. In short, the schema of treatment is roentgentherapy first, then nephrectomy and postoperative roentgentherapy.

FROM THE AUTHORS' SUMMARY.

CONGENITAL MALFORMATION OF THE UROGENITAL SYSTEM ASSOCIATED WITH DEFECTS IN THE ABDOMINAL MUSCULATURE. W. MAUERMAYER, Ztschr. Kinderh. **75**:671, 1955.

The syndrome of urogenital malformations, cryptorchidism, and absent or deficient abdominal musculature is reviewed, and a 19-year-old patient is discussed who presented the above syndrome with kidney insufficiency. A transurethral bladder-neck resection was performed which relieved urinary retention, but no changes occurred in the urea blood level.

GLASER, Baltimore.

AMBIGUOUS SEXUAL TYPES. ROBERT CLEMENT, Rev. españ. pediat. **9**:547 (May-June) 1953.

The outline of the type of examination necessary in children who are pseudohermaphrodites is given. The writer feels that the word pseudohermaphrodite should be dropped in favor of the term sexual ambiguity. In this paper he describes the various anomalies which may occur in the gynandrous type as differentiated from the androgynous individual. The newer methods of assaying the role of the suprarenals as well as the gonads make it possible and necessary to determine the dominant sex earlier, and this should be done very early for the psychological health of the individual.

The examination should include clinical examination of the external genitalia to determine whether plastic surgery will help. The amputation of the penis-like clitoris, however, is inexcusable, because if it is later discovered that the female gonad is functioning, this organ can be subjected to subinvolution by the use of estrogens.

Hormonal studies including 17-ketosteroids and psychological tests should be done over a period of time, watching for any changes.

Surgical exploration, if necessary, should be done to determine surgically and histologically the amount of function and the possibility for either copulation or gestation.

Parents should be told to choose a name which would be appropriate for either sex and the child should be made to feel that he is not a freak or an inacceptable individual.

Two case histories are included.

ALLEN, N. Mex.

PSEUDO PUBERTAS PRAECOX BY DIETHYLSTILBESTROL OINTMENT. C. HOOFT, J. BEKAERT and A. BLANCQUART, Maandschr. kindergeneesk. **22**:126 (April) 1954.

A 6-year-old girl with fluor albus was for one month treated by applying to the vulva an ointment containing 10 mg. diethylstilbestrol per gram. After swelling of the breasts and pigmentation of the areolae a vaginal bleeding occurred. There were no other signs of pubertas praecox except some hairs in the mons veneris.

Hormonal examination of the urine showed an increased excretion of estrogen (30 units per 24 hours) with normal quantities of gonadotropins, 17-ketosteroids, and 11-oxysteroids. The clinical picture was not typical for an adrenal tumor. The glandular tissue of the mammae regressed after stopping the treatment with the ointment.

VAN CREVELD, Amsterdam.

GENITAL INTERSEXUALITY IN THREE BROTHERS. O. M. DE VAAL, Maandschr. kindergeneesk. **22**:239 (July) 1954.

The different forms of intersexuality can be subdivided according to the etiology in four groups. These are (1) hormonal intersexuality, (2) gonadal intersexuality, (3) genetic intersexuality in genetically female individuals, and (4) genetic intersexuality in genetically male

individuals. The fourth group is, according to the literature, the most frequent. As a consequence of a disturbance in the development, especially of the genital tubercle, the genitals of a genetically male individual can have an aspect which is very similar to the female genitals. A family is described with four children. The oldest one was first seen when 6 years old. At birth there had been doubt about the sex, but it was decided that the child was a girl. After six years there proved to be present in the left "labium" a bean-sized testicle, and there was a cremaster reflex. The second child was a normal girl; in the third child there was again some doubt about the sex; at first it was thought to be a girl, but on the second day it was decided that it was a boy. The fourth child again was thought to be a girl, but after six months testicles were found in both "labia."

Clinically signs of virilism and of disturbances in the metabolism were absent. A remarkable fact in this family was that not only the parents were first cousins, but also the parents of the father and one pair of the grandparents of the father were first cousins.

VAN CREVELD, Amsterdam.

Diseases of Ductless Glands; Endocrinology

MAINTENANCE OF PREGNANCY IN THE ABSENCE OF DIETARY PROTEIN WITH ESTRONE AND PROGESTERONE. MARJORIE M. NELSON and HERBERT M. EVANS, Endocrinology **55**: 543-549 (Nov.) 1954.

The data presented in this study demonstrate that pregnancy can be maintained in all animals on a protein-free diet by injections of estrone and progesterone. Furthermore, the injection of either hormone separately can maintain pregnancy in the majority of the animals. The hormonal inadequacies of the protein-deficient rats are thus clearly shown.

JACOBSEN, Buffalo.

THE PRODUCTION OF HYPERTENSION, NEPHROSCLEROSIS AND CARDIAC LESIONS BY METHYLANDROSTENEDIOL TREATMENT IN THE RAT. ERNESTO SALGADO and HANS SELYE, Endocrinology **55**:550-560 (Nov.) 1954.

Experiments on intact rats, sensitized by unilateral nephrectomy and a high sodium intake, confirm earlier observations that methylandrostenediol (MAD) can produce a syndrome of hyalinosis (characterized by nephrosclerosis, periarteritis nodosa, and myocarditis, with hyalinized nodules in the heart) accompanied by hypertension and polyuria. All these changes are quite comparable to those which had previously been obtained with mineralocorticoids, such as DCA.

None of the above-mentioned pathologic changes are produced by MAD after bilateral adrenalectomy in similarly sensitized rats.

JACOBSEN, Buffalo.

BIOASSAY OF MINERALOCORTICOIDS: RELATIONSHIP OF STRUCTURE TO PHYSIOLOGICAL ACTIVITY. B. J. AXELRAD, J. E. CATES, B. B. JOHNSON and J. A. LUETSCHER JR., Endocrinology **55**:568-574 (Nov.) 1954.

Adrenal cortical extracts and human urine contain a corticosteroid of great potency measured by its effect on sodium and potassium excretion and on the survival of adrenalectomized animals.

In the search for corticosteroids with sodium-retaining activity a series of 32 compounds, related in structure to the adrenocortical hormones, have been tested for effect on excretion of sodium and potassium in adrenalectomized rats. Aldosterone, isolated from adrenal cortical extract, and a corticosteroid presumed to be aldosterone, extracted from human urine, are considerably more potent than any of the other compounds studied.

JACOBSEN, Buffalo.

THE EFFECT OF METABOLITES OF CHLORAMPHENICOL (CHLORMYCETIN) ON THE THYROID OF THE RAT. R. Q. THOMPSON, M. STURTEVANT, O. D. BIRD, and A. J. GLAZKO, Endocrinology **55**:665-681 (Nov.) 1954.

The data reported herein show that chloramphenicol exerts a goitrogenic action when administered in relatively large amounts to rats over extended periods. The experimental evidence would indicate that arylamines arising from the degradation of chloramphenicol in the rat are responsible for the goitrogenic activity observed.

JACOBSEN, Buffalo.

REVIEW: INSULIN (HYPOGLYCEMIC) REACTIONS IN DIABETIC PATIENTS. J. I. GOODMAN, Metabolism **2**:485 (Nov.) 1953.

The author reviews publications referring to hypoglycemic reactions to injection of insulin and discusses the clinical manifestations of hypoglycemia. The central nervous system is the most sensitive to hypoglycemia because of the fact that "the brain is the only organ that derives its energy exclusively from the combustion of dextrose."

The dangers of permanent cerebral damage following hypoglycemia are emphasized. Pathological studies of the brain following hypoglycemia reveal disintegration and disappearance of brain cells, both gray and white matter, congestion, petechial and extensive cerebral hemorrhages, patchy demyelinization, large areas of encephalomalacia and active proliferation, cyst formation, and gliosis. Definite cerebral damage may follow either large single doses of insulin or repeated hypoglycemia reactions.

Because of these harmful consequences of hypoglycemia the author advises the careful supervision of the administration of insulin to patients with diabetes, especially protamine zinc insulin, administration of which is not infrequently followed by untoward reactions. He warns against the overzealous practice of trying to keep patients sugar-free and prefers to err on the side of not giving enough insulin to risking the dangers of hypoglycemic reactions.

KAPLAN, Bethesda, Md.

PARADOXICAL HYPERGLYCEMIA IN DIABETIC PATIENTS TREATED WITH INSULIN. G. T. PERKOFF and F. H. TYLER. Metabolism **3**:110 (March) 1954.

The authors report observations on 10 patients with diabetes in whom it was found that hyperglycemia and glycosuria were relieved only by the reduction of the dose of administered insulin. Management of these patients was understandably difficult until the true state of affairs was recognized, since increasing the dose of insulin served only to aggravate the hyperglycemia and glycosuria.

A hint of the existence of this paradoxical effect of increasing insulin dosage may be provided by the observation that glycosuria decreases after meals.

KAPLAN, Bethesda, Md.

THE HOMOPLASTIC TRANSPLANTS OF FETAL ADRENAL GLANDS IN PATIENTS WITH SKIN DISEASES RESPONDING TO ADRENOCORTICOTROPIC HORMONE (ACTH) AND/OR CORTISONE H. C. TENG, ALVIN P. SHAPIRO, and ARTHUR GROLLMAN, Metabolism **3**:405 (Sept.) 1954.

Six patients with chronic skin diseases (pemphigus foliaceus, pemphigus vegetans, parapsoriasis, atopic dermatitis, disseminated lupus erythematosus, and seborrheic dermatitis) were studied. All had received large doses of ACTH or cortisone over prolonged periods of time. Following transplants of fresh human fetal adrenal tissue, the amounts of ACTH or cortisone required to control the disease were substantially diminished in four of the six cases.

KAPLAN, Bethesda, Md.

PSEUDO-HYPOPARATHYROIDISM. M. E. MACGREGOR and T. P. WHITEHEAD, Arch. Dis. Childhood **29**:398 (Oct.) 1954.

This is a description of three cases and a critical appraisal of earlier accounts of the disease.

The clinical features of pseudohypoparathyroidism, first defined and named by Albright and his colleagues, are described, examined, and contrasted with those of spontaneous hypoparathyroidism.

Using only the diagnostic criteria that are considered to be valid, 25 published accounts of pseudohypoparathyroidism have been collected.

Three new case reports are added to these, and some details are provided of another unpublished case. A group of 27 cases is then surveyed, and some other unproved cases possibly of the same type are described.

Certain difficulties were encountered in trying to reproduce the responses to parathyroid hormone that other workers have obtained in normal and pseudohypoparathyroid subjects, and the bearing of these upon the nature of the disorder is debated.

KELLY, Milwaukee.

CHRONIC IDIOPATHIC HYPOPARATHYROIDISM ASSOCIATED WITH MONILIASIS. MURIEL M. MCLEAN, Arch. Dis. Childhood **29**:419 (Oct.) 1954.

A case of chronic idiopathic hypoparathyroidism associated with moniliasis is reported.

The frequency with which monilial infection has been reported in idiopathic hypoparathyroidism indicates that it is more than a chance finding. It has not been reported in parathyroid deficiency following thyroidectomy, and in some cases it has preceded the appearance of symptoms of hypoparathyroidism.

It seems unlikely that the fungus infection is responsible for depression of parathyroid activity, but there may be some factor which depresses the parathyroids and also encourages fungus infections.

KELLY, Milwaukee.

THE BONNEVIE-ULRICH SYNDROME. A. J. KEAY and IAN C. LEWIS, Arch. Dis. Childhood **29**:424 (Oct.) 1954.

A new name, pterygolymphangiectasia or pterygolymphangiectatic infantilism, where gonadal hypoplasia is established, is suggested.

A typical case of the symmetrical form of the Bonnevie-Ulrich syndrome with, in addition, congenital hypertrophic pyloric stenosis, is recorded.

The American and European literature concerning the Bonnevie-Ulrich syndrome and its relationship to Turner's syndrome is discussed.

KELLY, Milwaukee.

THE USE OF THE INSULIN ZINC SUSPENSION IN DIABETIC CHILDREN. ARTHUR W. FERGUSON, Arch. Dis. Childhood **29**:436 (Oct.) 1954.

A study has been made of insulin zinc suspension (IZS) in 15 diabetic children.

In 14 of the 15 children it proved possible to obtain satisfactory control in hospital with one daily injection of IZS. Fourteen of the children have been observed as outpatients, and twelve of them have remained well stabilized, though changes in the dosage have been needed in four of them.

In three of the children maintenance of control with IZS was poor, in one child while in hospital and in two after returning home. All three had previously proved particularly unstable.

Four of the children were previously untreated, and all of these were eventually well controlled by IZS. Two of these were treated initially with IZS and responded well.

In nine children blood sugar control with soluble insulin and with IZS was studied for comparison. The control obtainable with one daily injection of IZS was in all of them at least equal to that given by two injections of soluble insulin.

There has been no evidence of deterioration in the activity of IZS during the study, and no evident reactions have occurred at the sites of injection.

KELLY, Milwaukee.

CRETINISM IN ONE OF MONOZYGOTIC TWINS. CONSTANCE C. FORSYTH, Great Ormond St. J. (No. 7) pp. 62-65 (June) 1954.

One of identical twins was found to be a cretin, when 2½ years old. At that age she showed a bone age of 9 months, compared to 2½ years for her sister, 8 teeth as against 20, and was 30 in. tall against 36 for her sister. Two years later the height difference was 2½ in., bone age normal, and number of teeth normal.

MCGUIGAN, Evanston, Ill.

COELIAC DISEASE AND DIABETES MELLITUS IN THE SAME PATIENT. W. W. PAYNE, Great Ormond St. J. (No. 3) pp. 118-122 (Winter) 1954-1955.

The author states that the association of celiac disease and diabetes in the same patient is extremely rare. The problems of the treatment of a 7-year-old boy with the two unconnected diseases are discussed.

MCGUIGAN, Evanston, Ill.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

AN UNUSUAL FORM OF OSSEOUS DYSPLASIA. R. MEYER, Am. J. Roentgenol. **73**:761-764 (May) 1955.

The case presented is apparently reported because it does not fit into any characteristic classification of the various groups of osseous dysplasia. It is somewhat similar to the forme fruste

of gargoylism; however, clinically there was sexual precocity in this child, which is different from what would be expected in a case of gargoylism.

The essential clinical findings were that of an apparently normal child until the age of 4 years, at which time rather marked weakness was noted, and at the age of 9 years the child's back began to develop a scoliosis. The child in addition was markedly retarded mentally.

Radiographically the mandible was abnormally small and the height of the lumbar vertebra was disproportionately greater than the transverse diameters. The intervertebral spaces showed some calcification, and the anterior portions of the bodies of D-10 through D-12 were fused to form an apex of a kyphotic curve. The phalanges were missing from several of the fingers and toes.

ALTMAN, Miami, Fla.

CHONDROECTODERMAL DYSPLASIA. H. WEISS and A. D. CROSETT JR., J. Pediat. **46**:268-275 (March) 1955.

In 1940 Ellis and van Creveld first described a syndrome of congenital defects that included ectodermal dysplasia, polydactyly, chondrodysplasia, and malformed heart. In 1952 Caffey reported two cases that fit this syndrome. He called attention to the short thick tubular bones and retarded skeletal maturation. The authors report a 9 month-old boy with this syndrome, the sixth case reported in the medical literature.

MACDONALD, Pittsburgh.

CONGENITAL ABNORMALITIES OF THE FEET. LAWRENCE A. DAVIS and WILLIAM S. HATT, Radiology **64**:818-825, 1955.

An attempt is made by the authors to formulate the radiological aspects of the commoner abnormalities, such as clubfoot, "rocker deformity," flat foot, metatarsus varus, and pes cavus. Emphasis is placed on the technique of obtaining proper roentgenograms. True views must be made of the foot without attempts to correct the deformity at the time the film is exposed. For the anteroposterior view it is best to have the knees held together. Roentgenograms of this group of congenital anomalies with appropriate "angles" illustrating the deformity accompany the article.

ANSPACH, Riverside, Ill.

THE EARLY RECOGNITION OF PREMATURE CRANIAL SYNOSTOSIS. JOHN W. HOPE, EUGENE B. SPITZ, and HARRY W. SLADE, Radiology **65**:183-193, 1955.

The first physical defect usually consists of an abnormally shaped head which frequently has a palpable ridge over the closed suture, with movement of adjacent skull bones impossible. Exophthalmos is a frequent sign in the presence of a shallow anterior fossa. Because of relatively few physical findings the roentgen examination is of great importance. The suture which will close prematurely is very narrow, at times the bone is heaped up on each side of the suture. Abnormal contour of the skull is often present before closure of the sutures occur. Later, after closure, the intercranial pressure may reach 500 mm. of water. This causes thinning of the inner table of the vault and an increase of the prominence of convolutional markings. Sometimes penetration of the skull tables occurs, and herniation of the brain may take place. Illustrations of five cases of synostosis are presented.

ANSPACH, Riverside, Ill.

TREATMENT OF CONGENITAL EQUINOVARUS ACCORDING TO THE DENIS BROWNE METHOD. E. ROVIRALTA and J. PICONOL, Acta pediat. españ. **13**:35-46 (Jan.) 1955.

The authors review the treatment of congenital equinovarus according to the method of Denis Browne. They include many illustrations of cases followed for a period of five years. Twenty-eight cases were treated. The authors state that after the definite diagnosis is made the treatment should be started immediately. Six of the cases were started between the 5th and 15th days after birth. The treatment should be carefully and slowly done, with due consideration of soft tissue, and cover five years.

ALLEN, Santa Fe, N. Mex.

Diseases of Eye

NEURORETINITIS FOLLOWING MEASLES. R. H. BEDROSSIAN, J. Pediat. **46**:329 (March) 1955.

The patient was a 6-year-old white girl. She had measles followed a week later by mild headache, pain on moving her eyes, and loss of vision. This is an unusual case of neuronitis following measles, with severe loss of vision but with little or no evidence of encephalitis.

MACDONALD, Pittsburgh.

RETROLENTAL FIBROPLASIA FOLLOWING PROTRACTED USE OF OXYGEN AT LOW CONCENTRATION. J. STEPANIK, Wien. klin. Wchnschr. **67**:481-483 (July 1) 1955.

A group of premature infants were exposed in incubators from two days to eight weeks to 35% to 50% oxygen. In two cases a mild degree of retrolental fibroplasia developed. Abstention from continuous use of oxygen is recommended; it should only be resorted to for overcoming cyanosis. It is not to be used for a longer period of time than necessary to overcome the cyanosis. The concentration of oxygen should not exceed 40%.

AMBERG, Rochester, Minn.

Cutaneous Diseases; Allergy

STRAINED MEAT FORMULAS IN ALLERGIC DISEASES OF INFANTS AND CHILDREN. ALBERT ROWE JR. and ALBERT H. ROWE, California Med. **81**:279 (Oct.) 1954.

Strained-meat formulas containing approximately the protein, carbohydrate, fat, and mineral content of cow's milk have proved valuable in the study of animal milk allergy in infants and children.

Strained-meat formulas have been given to over 100 infants and children with bronchial asthma, eczema, and gastrointestinal allergic disease. There were no instances of weight loss or anemia. Clinical improvement was evident in most cases.

PRYOR, Redwood City, Calif.

CORTICOTROPHIN, CORTISONE, AND HYDROCORTISONE IN DISEASES OF HYPERSENSITIVITY: I. BIOLOGICAL CORTICOID EXCRETION DURING ACUTE SYMPTOMS. B. ROSE, T. W. FYLES, and E. H. VENNING, J. Allergy **26**:1 (Jan.) 1955.

This study was done to learn whether or not there is a relative pituitary or adrenal insufficiency in asthma and whether the allergic patient is incapable of responding to the stress of his disease with an increase in adrenal activity. The urinary glucocorticoids were assayed.

There were 58 patients with active asthma. Persistence of symptoms is not associated with a rise in the level of glucocorticoid excretion. Spontaneous recovery through rest and recovery induced by nonspecific therapy are associated with a rise in urinary corticoid excretion.

The results suggest that the asthmatic patient may excrete smaller quantities of urinary corticoids than do normal subjects, and that the persistence of symptoms may be due in part to an inability of the pituitary or adrenal to augment the output of corticoids or to respond to the stimulus of asthma. The results in two cases of urticaria and nine of atopic dermatitis do not differ significantly from those found in normal subjects, and in this respect they differ from the asthmatic patients.

HOYER, Cincinnati.

BRONCHIAL ASTHMA UNRELATED TO POSITIVE SKIN REACTIONS: A PSYCHOSOMATIC STUDY. HYMAN MILLER and DOROTHY W. BARUCH, J. Allergy **26**:54 (Jan.) 1955.

The patient was a 3-year-eight-month-old boy, the second of three children. He was frail and timid, and his chest was typically asthmatic.

He had 3+ and 4+ positive skin reactions to pollens, many inhalant substances, and many foods; the reaction to egg white was most marked.

He had 12 episodes of wheezing during a 10-month period. There was no correlation between the pollen count and climatological data. There was no restriction of diet. The mother, father, and patient had many psychotherapy sessions during the 10-month period of observation.

It was found that the attacks of "wheezing coincided with the inability on the part of the patient to openly express the anger which occurred when he felt deprived of or threatened by the loss of parental affection."

When his anger was expressed and he was made to feel secure in his expression of it, his asthma could be aborted, or, when present, cleared.

His emotional problems were expressed somatically as clinical allergy which functioned within a pattern set by his allergic constitution quite independently of his exposures to reacting allergens.

HOYER, Cincinnati.

ALLERGINS IN VEGETABLE OILS. A. F. ESSELLIER, P. JEANNERET, H. R. MARTI, and H. ROSENMUND, J. Allergy **26**:107 (March) 1955.

Tripalmitin, 0.1 cc. applied daily by scarification, produced no reaction or change in total leucocyte or eosinophile count in an experiment lasting five weeks.

Butyric acid, 0.1 cc., was injected subcutaneously daily. The experiment was discontinued after two weeks because of painful local reactions each time. There was no change in total leucocyte or eosinophile count.

Tributyrin, 0.1 cc., was injected subcutaneously daily for three weeks. The injection was painful each time, and there was also a slight local reaction. There was no change in total leucocyte or eosinophile count.

Triolein, 0.1 cc., was injected subcutaneously daily. After the 28th day there developed an area of redness 8 mm. in diameter. This type of reaction occurred with each succeeding injection, and with these later injections there was an analogous reaction at the site of previous injections, where there had been no reaction previously. The total leucocyte and eosinophile count showed no significant change.

The authors believe that sensitization by natural vegetable oils can be attributed to fatty acid triglycerides and not to impurities.

HOYER, Cincinnati.

HYDROCORTISONE OINTMENT IN THE TREATMENT OF INFANTILE ECZEMA. LEWIS WEBB HILL, New England J. Med. **252**:1038 (June 16) 1955.

The author reports his experiences with 110 infants and children suffering from atopic or contact dermatitis. The hydrocortisone ointment used was 1% strength in most instances, and the areas treated were generally not extensive, e. g., the cheeks. The material is expensive, but the author points out that a great deal of ointment can be purchased for the price of a days' hospitalization.

Preexisting infection is a contraindication to the use of hydrocortisone ointment. The material is most effective in superficial scaly or erythematous areas and of little value for deep-seated papules or thick crusts.

The author regards this steroid preparation as a valuable addition to the helpful aids in childhood eczema, but not a complete substitute for local remedies of traditional value.

WHEELOCK, Washington, D. C.

A NEW APPROACH TO THE LOCAL TREATMENT OF ALOPECIA AREATA. HARRY M. ROBINSON and RAYMOND C. V. ROBINSON, South. M. J. **47**:894 (Sept.) 1954.

Benzyl benzoate as a 50% oil in water emulsion in 25% solution combined with tyrothricin gave good results in 90% of patients being treated for alopecia areata. The medications were massaged into the scalp daily for 8-42 weeks. Two patients had to discontinue treatment after a week because of contact dermatitis.

LOGAN, Rochester, Minn.

THE USE OF ACTH AND CORTISONE IN CHILDHOOD ALLERGIES. C. COLLINS-WILLIAMS, Canad. M. A. J. **72**:776-777 (June 20) 1955.

The author points out that although ACTH and cortisone are very useful in treating the major allergies of childhood, namely, asthma, hay fever, eczema, and urticaria, they have definite limitations and should not be used as replacements for accepted methods of antiallergic therapy.

McGUIGAN, Evanston, Ill.

HEPATIC NECROSIS IN DISSEMINATED HERPES SIMPLEX. R. C. B. PUGH, G. H. NEWNS, and J. A. DUDGEON, Arch. Dis. Childhood **29**:60 (Feb.) 1954.

A fatal case of disseminated herpes simplex in a newborn infant is described. The oropharynx is suggested as the site of primary infection. Visceral lesions were confined to the liver, and their herpetic etiology was established by the pathological findings and isolation of virus. A marked difference was found in the serum antibody titer between mother and child.

KELLY, Milwaukee.

EPIDERMOLYSIS BULLOSA LETHALIS. C. D. CALNAN, Great Ormond St. J. (No. 3) pp. 113-117 (Winter) 1954-1955.

Two fatal cases of recessive epidermolysis bullosa are described. In both cases the girls were 6 months old, and at birth both were noted to have some shedding of skin on a few fingers around the nails. The progress, treatment, and investigation of the two cases are discussed.

McGUIGAN, Evanston, Ill.

"FORBINA," A NEW DUSTING POWDER FOR INFANTS. R. ALBANESI, Minerva pediat. **6**:661 (Aug. 31) 1954.

"Forbina" is a dusting powder containing 1% formocibazol, a chemical combination of formaldehyde and sulfathiazole. The author found it efficacious in cases of eczema, seborrhea, and intertrigo. No evidence of sulfonamide drug was found in either the blood or the urine of 36 infants upon whose skin the powder was used.

HIGGINS, Boston.

ACRODYNIA: ETIOPATHOGENIC AND THERAPEUTIC CONSIDERATIONS. FREDERICO MARTINEZ PEREZ, Rev. españ. pediat. **10**:27-39 (Jan.-Feb.) 1954.

The author presents three cases of acrodynia with all the classical clinical symptoms. In one case, however, mercury was not isolated in the urine, although the history showed sensitivity to mercury. This case recovered most rapidly with BAL.

The history of the disease and the forms it takes are described, and considerable discussion is devoted to the three theories as to etiology. These are infectious, toxic (mercury or other heavy metals), and vitamin B deficit.

The author also discusses the pathology and the rationale for the use of vitamin B, BAL, and ACTH and cortisone in cases resistant to other forms of treatment.

Diagnostic signs considered essential other than skin manifestations are hypertension, tachycardia, and hyperglycemia. In cases where there is excessive sweating the possibility of a hypokalemia must be kept in mind.

ALLEN, Santa Fe, N. Mex.

REPORT OF THREE CHILDREN WITH THE MALIGNANT FORM OF ERYTHEMA MULTIFORME EXUDATIVUM (STEVENS-JOHNSON SYNDROME). GERHARD BUCHA, Monatsschr. Kinderh. **103**:184-187 (March) 1955.

The author described three children with this disease. In addition to the characteristic exanthemata, severe stomatitis, and generalized mucous membrane involvement, severe diffuse bronchopneumonia occurred. The author believed that this was due to involvement of mucous membranes of the bronchial tract. Treatment with penicillin in high dosage was successful in all three patients, comparable to the treatment of any sepsis due to staphylococci or streptococci. Blood transfusions were also given to all three children and were thought to have been beneficial. Chloramphenicol was deemed a therapeutic failure in all three patients.

HARTENSTEIN, Syracuse, N. Y.

News and Comment

GENERAL NEWS

Specialists Certified by The American Board of Pediatrics, Inc.—The following physicians were certified as specialists by The American Board of Pediatrics, Inc., in Washington, D. C., on Dec. 2, 3, and 4, 1955.

Allen, Richard J., Bogota, N. J.
Allen, Wayne H., Sayre, Pa.

Barber, Joan Kay, Bronxville, N. Y.
Battle, William Clement, Huntington Station, N. Y.
Benson, William F., Brownwood, Texas.
Blodgett, Frederic M., Boston.
Bock, Charlotte Elizabeth, Medford, Mass.
Brinsfield, Dorothy Emily, Atlanta.
Busch, Edwin Stanley, Milwaukee.

Cabos, Else, San Francisco.
Caldwell, Tom O., Birmingham, Ala.
Cason, Louise, Miami, Fla.
Combs, Walter A., Washington, D. C.
Crooks, Robert D., Parkersburg, W. Va.
Cullina, Joseph C., West Hartford, Conn.

Davis, William Hersey, Jr., Winston-Salem, N. C.
Dunphy, Donal, New York.
Dusenberry, Charles, Huntington Station, N.Y.

Edwards, F. Kathryn, Decatur, Ga.
Erlandson, Marion Ellen, New York.
Evans, Martin Jay, Lawrence, L. I., N. Y.

Fairchild, Robert Charles, Mission, Kan.
Ferber, Jerome, Cresskill, N. J.
Francis, Yvette Fay, St. Albans, L. I., N. Y.

Garfunkel, Joseph M., Philadelphia.
Gilbert, Enid Fischer, Bethesda, Md.
Goldzier, Sanford Elias, II, East Meadow, N. Y.
Goodman, Morris, Binghamton, N. Y.
Gorvoy, John David, Bellerose, L. I., N. Y.
Gregory, Warren Collins, Winchester, Va.
Gursky, Andrew, Pittsburgh.

Hales, C. W., Columbus, Ohio.
Harris, Virginia Goddard, Syracuse, N. Y.
Herndon, Robert E., Chickasha, Okla.
Hopkins, Edward W., Baltimore.

Iezzoni, Domenic Gabriel, Cleveland.
Irwin, Richard M., Washington, D. C.

Jaffe, Vita R., Bethesda, Md.
Johnson, Oscar Leonard, Lake Jackson, Texas.
Joseph, Andre Camille, Nashville, Tenn.

Kaiser, Theodore Herbert, Aberdeen, Md.
Kantor, Howard L., Syosset, L. I., N. Y.
Kluger, Sheldon Howard, Wilkes-Barre, Pa.
Korn, Robert Lawrence, Clayton, Mo.
Kugel, Robert B., Baltimore, Md.

Lachman, Joseph, Chester, Pa.
Lipow, Herman William, New York.
Lonsway, Maurice J., Jr., Clayton, Mo.

Morton, Helen Luella, Richmond, Va.

Oast, Samuel Poindexter, III, Syosset, N. Y.
Osborne, Maurice M., Jr., Brookline, Mass.
Ownby, Ralph, Jr., Richmond, Va.

Pijan, Margaret Emma, Minneapolis.

Quinn, Norman James, Ambler, Pa.

Rhyne, Jimmie Lee, Lumberton, N. C.

St. Martin, David A., Silver Spring, Md.
Saunderson, Robert W., Jr., Salisbury, Md.
Simmons, Frederic Rudolph, Albany, Ga.
Sinnette, Calvin Herman, East Elmhurst, N. Y.
Smith, Arthur Gene, Rome, N. Y.
Sutherland, Betty Steele, Newton, Mass.
Sutherland, James McKenzie, Newton, Mass.

Tepper, Jason Alvin, Schenectady, N. Y.
Thalheim, Andrew Henry, Jr., Gretna, La.

Vogl, Charles, Columbia, S. C.

Williams, Margaret Lyman, Drexel Hill, Pa.
Willingham, Richard Baynard, Knoxville, Tenn.
Wojcik, Ladislas Dolores, Marion, Ind.

Ylitalo, William Henry, Madison, Wis.

Zinkham, William H., Baltimore.

Polio Vaccination: WHO Study Group Meeting.—Approximately 10,000,000 children in five countries have been vaccinated against poliomyelitis with no ill effects, apart from the comparatively few cases in the United States which were traced to the use of certain batches of faulty vaccines.

Polio vaccine of the Salk type has been shown to give good protection to children between the ages of 6 to 10 years. This is the only age group for which sufficient evidence is available to allow a definite opinion to be expressed. It is not yet possible to say how long the immunity conferred by vaccination can last.

These facts were brought out by the Study Group on Poliomyelitis Vaccination, called by the World Health Organization (WHO) for a five-day meeting in Stockholm. A 40-page report was prepared by the group and will be submitted to the Director-General of the World Health Organization; he will decide how it can best be used for the guidance of health authorities all over the world.

In the opinion of the group, the latest developments in production techniques and methods of testing of vaccines should be a further assurance of the safety of the product. Great importance should, however, be given to the continuing need to apply stringent safety tests to all lots of vaccine produced.

The scientists made a critical review of the methods at present in general use to ensure the harmlessness of polio vaccine and included in their report a number of highly technical comments concerning current safety-testing procedures.

In its report the group attempts to give as much guidance as possible to national health authorities who may be considering whether or not to begin polio vaccination programs.

The report mentions two main considerations on which any decision of this kind should be based. They are (1) the seriousness of the existing polio situation in the country concerned, particularly with regard to the paralytic form of the disease, and (2) the cost and practicability of a vaccination program considered in relation to the funds and facilities available and to the saving in human suffering and in the cost of hospital and social care which may result.

As a general rule, the members recommended that countries with a high incidence of poliomyelitis of the dangerous paralytic form should plan to bring vaccination into routine use at an early date. In countries with a low incidence of paralytic polio, a decision to vaccinate on a large scale should only be made after a careful review of all the relevant circumstances.

Recognizing that in a large number of countries there was only very scanty information available concerning the seriousness of poliomyelitis, the group also recommended what studies and surveys should be undertaken in order to furnish national health authorities with the basic information they needed in this matter.

Among the important questions discussed by the scientists was that of whether certain inoculations, and particularly those which cause severe local reaction, could have a "provocative" effect which in some way increased the dangers of poliomyelitis infection. It was agreed that such a "provocative effect" did in fact exist.

The group also dealt with the very important question of the strains of virus which should be used in the production of vaccines and listed the characteristics which should be sought in these virus strains. Detailed examination was also made of a large number of other technical questions connected with the laboratory processing and testing of vaccines.

Among the group's recommendations to the World Health Organization are several concerning valuable lines of research which should be followed. Members attached great importance to information presented to them concerning the progress of research on a new "living virus" type of vaccine different in principle from the "inactivated virus" vaccine of Dr. Salk. It was agreed that the "living virus" vaccine was still in an early and experimental stage of development but that work on it should be encouraged.

The persons attending the meeting were as follows:

Dr. Karl Evang
Director-General of Health Services
Oslo

Prof. S. Gard
Karolinska Institutet, School of Medicine
Stockholm

Dr. W. L. M. Perry
National Institute for Medical Research
London

Prof. E. T. C. Spooner
London School of Hygiene and Tropical Medicine
London

Dr. J. H. S. Gear
South African Institute for Medical Research
Johannesburg

Dr. F. P. Nagler
Department of National Health and Welfare
Ottawa

Dr. H. von Magnus
States Seruminstitute
Copenhagen

Prof. P. Lépine
Institut Pasteur
Paris

Prof. R. Haas
University of Freiburg
Freiburg

Dr. A. D. Langmuir, Chief
Epidemiology Branch
Communicable Disease Centre
Atlanta, Ga.,

Prof. J. R. Paul
Yale University School of Medicine
New Haven, Conn.

Dr. A. B. Sabin
Children's Hospital Research Foundation
University of Cincinnati College of Medicine
Cincinnati

ANNOUNCEMENTS

First International Congress on the Pathology of Infection.—The First International Congress on the Pathology of Infection will be held in Lyon, on May 24, 25, and 26, 1956, at the Combined Faculties of Medicine and Pharmacology, 8, avenue Rockefeller. The subjects of the program are the following:

1. Viral Neuroinfections

Ramon, of Paris: Rabies, Epidemiology, Immunology, Prophylaxis.
Pette, of Hamburg: Animal Experiments in the Investigation of Neuroviral Diseases.
D'Alessandro and Dardanoni, of Palermo: Etioepidemiological Aspects of Viral Neuritis.
Mollaret, of Paris: Recurrent Meningitis Caused by Ultravirus.

2. The Collagen Diseases in Infections

Fanconi and Rossi, of Zurich: The Clinical Aspects of the Collagen Diseases and the Etiopathogenic Importance of Bacterial Infections.
Delaunay, of Paris: The Mucopolysaccharide Collagen Connections Within the Connective Tissue Network and Their Importance in the Causation of Collagen Diseases.

In connection with the Congress, a Round Table Discussion on Rabies will be held on Friday, May 25, beginning at 3:30 p. m., under the presidency of Dr. Remlinger; it will be concerned with the following subjects: Antirabic Serum, Flury's Virus, and drafts of the International Sanitary Convention.

On Sunday, May 27th, the following will be held:

9 a. m.—A session of the Lyonese Society of Pediatrics, at the Children's Clinic, Hospital Edouard Herriot.

10 a. m.—A session of the Society of the Veterinary Sciences of Lyon will be held at the Veterinary School, 2, quai Chauveau.

Authors who wish to present papers are requested to indicate the title of their communication to the Secretariat of the Congress immediately.

Registrations will be received from now on at the Secretariat of the Congress: Institut Pasteur de Lyon—77, rue Pasteur, Lyon (France). The address is Ier Congrès International de Pathologie Infectieuse, 77, rue Pasteur—Lyon 1327-41.

The prices of registration are as follows:

Active Members (registration fee and the book containing the transactions of the Congress)..... 5000 French francs
Associate Members (persons accompanying those participating in the Congress)..... 3000 French francs
Registration for the banquet at the close of the session..... 2500 French francs

President of the Organization Committee: Sédallian of Lyon.
Secretaries of the Congress: Dr. Monnet, Dr. A. Bertoye, M. Carraz.
Treasurer: Dr. J. Viallier.

Public Health Scholarships.—The Harvard University School of Public Health announces that Public Health Scholarships for the academic year 1956-1957 will be granted to individuals of high professional promise in awards ranging from part tuition to tuition plus a stipend, according to the qualifications and financial needs of the applicants. The scholarship funds are limited and are primarily intended for citizens of the United States. In general, preference will be given to applicants under 35 years of age.

Scholarships are available to applicants in the following categories: physicians, dentists, and veterinarians; industrial physicians; public health nurses with a college degree and satisfactory field experience; social workers with a master's degree from an approved school of social work and acceptable experience in the field of medical or psychiatric social work; health educators with a college degree, training either in health education or in the natural and social sciences, and experience in general education or community health work; dietitians with a college degree and satisfactory field experience; college graduates who have concentrated in one of the natural sciences or in engineering (environmental aspects), for example, biologists, biochemists, nutritionists, microbiologists, parasitologists, or biostatisticians.

Scholarship applicants must be eligible for admission to the school as a candidate for one of the following degrees: MASTER OF PUBLIC HEALTH, DOCTOR OF PUBLIC HEALTH, MASTER OF SCIENCE IN HYGIENE, DOCTOR OF SCIENCE IN HYGIENE, MASTER OF INDUSTRIAL HEALTH.

A catalogue of the school, admission and scholarship applications, and further information may be obtained by writing the Secretary, Harvard School of Public Health, 55 Shattuck St., Boston 15.

Scholarship applicants must return completed admission and scholarship applications to the Harvard School of Public Health by **March 1, 1956.** Scholarship awards will be announced May 1, 1956. Under exceptional circumstances awards will be made at other times.

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References: 1. Youngblood, V. H.: J. Urol. 70:936, 1955. 2. Carroll, G.: Pediat. Clin. N. America, 1955, pp. 781-791.

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*Shwachman, H., Children's Hospital, Boston, The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Butler, A., Harvard Medical School, private communication.

Royce, S., Los Angeles Hospital, private communication.

Clay, W. A., Frank, D. W., and Logan, V. W., Studies on the Therapy of Pancreatic Insufficiency, Gastroenterology, 26: 169, 1954.

Everson, T. C., Grossman, M. I., and Ivy, A. C.: Bulletin of Amer. College of Surgeons, January, 1950.

Gibbs, G. E., Bradley, J. E., and Minot, J. V., Diagnosis and Treatment of Cystic Fibrosis of the Pancreas, J.A.M.A. 145: 1187 (1951).

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1. Ratner, B. et al: A.M.A. Am. J. Dis. Child. 89:187, 1955.
2. Glaser, J., and Johnstone, D. E.: J.A.M.A. 153:620, 1953.

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---

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3. Sherman, H. C.: Food Products, ed. 4, New York. The Macmillan Company, 1948, p. 221.

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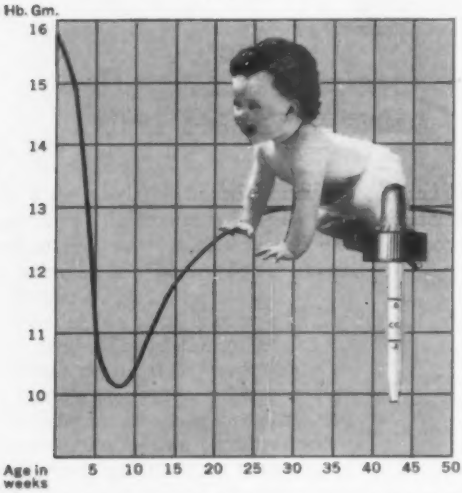

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(1) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86: 553, 1953. (2) Smith, C. H.: Bull. New York Acad. Med. 30: 155, 1954. (3) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1: 275, 1953. (4) Sturgeon, P.: Pediatrics 13: 107, 1954.

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